Section of Neurology

President W H McMenemey MD FRCP

Meeting February 16 1961

Hughlings Jackson Lecture

The Neurology of Language

by Sir Russell Brain Bt DM FRCP (*London*)

Introduction

This year happens to be a triple centenary, for in 1861 Hughlings Jackson published his first paper, Henry Head was born, and on April 18 Broca (1861) reported to a meeting of the Anthropological Society of Paris his aphasic patient who was to have such a profound and lasting influence on thought about aphasia. It seems to me appropriate, therefore, to commemorate in this lecture not only Hughlings Jackson, but also his two contemporaries, and particularly Henry Head. To-day when discussing the neurology of language it is difficult to dissociate Jackson and Head. Head's thought was entirely Jacksonian in spirit, and he repaid the debt by making Jackson's views more widely known and developing and extending them.

We may note in passing how very slender to-day seems the anatomical basis for Broca's ideas, for the patient from whom he inferred that the lesion of the frontal lobe was responsible for the loss of speech, had a softening of the left cerebral hemisphere which not only involved the greater part of the frontal lobe but produced a cavity the size of a hen's egg, which extended backwards as far as the ascending parietal convolution, below to 'the marginal convolution' of the temporosphenoidal lobe, and in its depth involved the insula and 'the extraventricular nucleus of the corpus striatum'.

It may be said, with some truth, that the correct theoretical interpretation of aphasia is of little clinical importance, and will not make it any easier to localize a cerebral lesion. Both Jackson and Head, however, saw its wider implications. Since speech is a distinctively human characteristic, when we study its organization in the nervous system we are looking at something which is of the essence of human nature, and of the relationship between the brain and the mind. Moreover, we cannot consider the effects of brain lesions upon language without encountering the general problem of cerebral representation and localization. At two points, therefore, the neurology of language touches fundamental problems of neurology.

The first seven chapters of the first volume of Head's 'Aphasia' (1926) are a critical review of the subject up to the time at which he was writing. The sixth is entitled 'Chaos', and if Head could have foreseen the conflicting views still being expressed about aphasia to-day, he would hardly have found the situation more orderly than it was then. I shall not review past ideas in any detail, but before I come to the present, and the future, I want to consider briefly what seems to me to be the cause of the chaos, why it is possible for workers in this field still to have such conflicting views, and why no current interpretation of aphasia seems entirely satisfactory. This, I suggest, springs from the unique nature of speech, which functionally must be considered both psychologically and physiologically. As Jackson (1878, p. 313) put it, 'speech and words are psychical terms; words have of course anatomical substrata or bases as other psychical states have. We must as carefully distinguish betwixt words and their physical bases as we do betwixt colour and its physical basis; a psychical state is always accompanied by a physical state, but nevertheless the two things have distinct natures'.

The most elementary unit of speech is the phoneme, each of which is a particular kind of speech sound, and since printed letters may be sounded in different ways there are more phonemes than letters in the alphabet, and they have distinctive symbols in phonetics. A phoneme, however, is an abstract idea, for each person pronounces the same phoneme in a different way from everyone else. So we have to give a different name to the actual sounds produced in speech – phones, and say that a phoneme is a category of sounds which embraces all sufficiently similar phones (Brown 1956). Both phones, which are sounds, and phonemes, which are categories of sounds, are psychological entities. So, of course,

are groupings of phonemes into words, and words into sentences, and names and meanings. And, when speech breaks down in aphasia, this breakdown presents itself in the form of a psychological disorder. When we say that the patient cannot say what he means, or understand what he hears, we are using psychological terms to describe what is wrong.

Aphasia then is a psychological disorder, but it presents itself to the clinician as a symptom of an anatomical lesion, usually focal. What is the relationship between them?

Historically it is possible to recognize three main schools of thought on this question:

(1) The first view is the naïve psychoanatomical. In the broadest sense we all aim at a psychoanatomical account of psychological activities, that is at establishing the most detailed possible correlation between the mind and the brain. The naïve psychoanatomical view, however, assumes that there is a direct relationship between psychological functions and localized areas of the brain. It follows from this that localized lesions of the brain can and do produce limited defects, which correspond to psychological functions. There have been many exponents of this view from Bastian (1898) in the early days through Henschen (1920, 1922) in an intermediate period up to Kleist (1959) at the present day. But I will illustrate it by quoting Charcot (1887) whose views on aphasia are perhaps a little less familiar. Charcot said that a word is a complex composed of four fundamental elements, an auditory image, a visual image, and two motor images, one articulatory and the other graphic. There may be an amnesia for any one of these or for a combination of them and therefore 'it follows that the various groups of memories have their seat in certain localized regions of the brain'. Here then are words analysed into supposed psychological factors – remembered images, each variety of which is naïvely regarded as localized in a particular anatomical region of the brain. The best way to recognize the defects of this kind of approach will be to see what is involved in a more satisfactory one, but Hughlings Jackson implicitly criticized the naïve psychoanatomists when he said, in a continuation of the passage quoted above: 'We must not say that the "memory of words" is a *function* of any part of the nervous system, for function is a physiological term' (Jackson 1878, p. 313) and 'a method which is founded on classifications which are partly anatomical and physiological, and partly psychological, confuses the real issues (Jackson 1878, p. 306).

(2) In contrast to the naïve psychoanatomical view, there are the clinical psychologists. Their interest is concentrated on the description of the psychological disturbance of function in aphasia, while the relationship of this to anatomy is largely neglected, or a vaguely holistic view is proposed. We owe a double debt to the many workers, ultimately disciples of Jackson and Head, who belong to this school – a negative one, for all that they have done to expose the inadequacies of the naïve psychoanatomists, and a positive one, for preparing the ground for a psychological interpretation which is now beginning to yield a rich harvest. But they have done little to advance our knowledge of the fundamental problem of the relationship between the mind and the brain in the sphere of speech. Goldstein (1948), for example, who owes much to Jackson and has added a great deal to our understanding of aphasia as a psychological disturbance, when it comes to anatomy writes, 'as much as the rejection of the old concept of circumscribed localization is justified, such a rejection is not in contradiction to an assumption that to each performance corresponds an excitation of definite structure in the cortex, indeed, not in a circumscribed area but widespread over the whole cortex, differently in each performance. This is what we should term localization'.

Head (1926) himself well illustrates the dilemma in which the clinical psychologist finds himself. His classification of the aphasias was psychological, for he recognized four groups characterized predominantly by defective word-formation, defective syntax, defective naming and defective comprehension of the significance of words and phrases as a whole – all psychological disorders. But when he comes to cerebral localization he becomes involuntarily a naïve psychoanatomist, for in spite of all his protestations against 'the diagram-makers' he correlates each loss of a specific psychological function with a localized anatomical lesion.

(3) The third historical school of thought on aphasia may be described as the empiricist. This abandons the attempt to *interpret* the relationship between the psychological disorder present in aphasia and the anatomical situation of the lesion. It is content to say that certain forms of aphasia can be recognized *clinically* by the disorders of function which characterize them. Members of this school may differ about the number of distinct forms which they recognize but they are apt to agree that recognizable forms tend to merge into one another. To emphasize their empiricism they are likely to describe the varieties of aphasia eponymously as, for example, Broca's aphasia or Wernicke's aphasia, in order to avoid any suggestion of a psychological interpretation. Even the empiricist school, however, does not escape all difficulties, more particularly when it comes to localization, for although there exists a rough

relationship between a particular clinical variety of aphasia and a lesion in a certain situation in the brain, exceptions to these correlations are notorious, and are well illustrated by Conrad's observations (1954) on the wide scatter of the lesions responsible for Broca's aphasia and pure word-dumbness.

Most students of aphasia can be classified in one or other of these three schools, none of which, however, provides a very stable position. Hybrid descriptions are common, such as 'subcortical motor aphasia', which is a blend of anatomical, physiological and psychological concepts. Physiological terms, such as 'motor' and 'sensory', occur in the literature from time to time, but historically at least scarcely justify the recognition of a physiological school of thought.

I suggest that the source of all this confusion is the failure to recognize that speech involves a three-term relationship, or a description at three levels, and an understanding of the relationship between them: these are the psychological, the physiological, and the anatomical. An anatomical lesion of the brain, if it disturbs speech, does so by disorganizing the physiological functions upon which speech depends. This leads to an associated psychological disorder. If we try to interpret the neurology of speech solely by means of observations made on aphasic patients, we are hampered by having to deal with two unknowns – the relationship of psychological to physiological function, and the relationship of physiological function to anatomical structure. Moreover, studies of the neurology of language based solely upon aphasia seem exposed to the logical difficulty that if we begin by inferring the normal from the pathological, we cannot then use it to explain the pathological. On the other hand, if we can establish some independent basis for the physiology of language, we can use that to interpret aphasia, and the study of aphasia to enlarge and enrich it.

The Development of Speech in Infancy

The first source of information about the psychophysiology of speech is the study of the development of speech in infancy, about the course of which there is general agreement. I need now draw attention only to certain features. The third stage of infant vocalization is *babbling*, which usually begins towards the end of the second month. The fact that the normal child hears the sound which it produces is of great importance for the further development of its speech. Children born deaf begin to babble, but soon cease to do so. Bühler (1930) says, 'the psychologically important fact is the formation of strong associations between the auditory impression and the movements which produce it, for this is the essential basis of the later imitation of the sounds the child hears, in which it has to translate what it has heard into vocal movements of its own'. As Froment (1935) well puts it, 'it is by trial and error guided by the ear that the baby learns all articulatory processes'. He compares it with a violinist tuning his instrument. We are familiar enough with the general importance of afferent impulses from muscles for the regulation of movement: speech is influenced by auditory impulses as well, and both are produced by its motor element. Thus at this early stage, and hence fundamentally, speech is a sensorimotor-sensory activity but, whereas congenital deafness interferes grossly with the development of speech, when once normal speech has been established acquired deafness disturbs it relatively little. Observations have recently been made on the effects of artificial disturbances of what has been termed 'the auditory feedback' (Lee 1950, Black 1951). If a person's own speech is played back to him after a short delay through closely-fitting headphones, his rate of speaking becomes slowed, and other disturbances appear. There is more than one possible explanation of this.

But, to return to the developing child, Eisenson (1938) points out that after it has learned to imitate many sound combinations of its own accidental making, it has laid the foundations for the next step in the development of speech, *echolalia*. This is the imitation by the child of sounds which it hears others make, but which it does not itself understand, and this stage of speech begins at about the ninth or tenth month. As Eisenson says, during this stage, 'the child acquires a repertoire of sound complexes which ultimately he will come to be able to produce at will, and which he must have before he can learn to speak, or acquire a language, in the adult sense'.

But echolalia is a highly complex process. We say that the child imitates sounds made by others, but what we call *the same sounds*, made for example by its father and its mother, though they may both be the same phoneme, are composed of phones which differ in pitch as well as in other characteristics, and which therefore constitute very different physical stimuli; and the sound which the infant makes, if it successfully imitates them, is a sound yet again of a different pitch, which must therefore sound different to the child itself. Already at this early stage of speech development, therefore, the child is learning to recognize and reproduce the phoneme – a pattern which is common to the sounds made by its parents and by itself, although in other important respects these sounds differ from each other. We need not now consider the probably complex process of learning which leads to this result: in physiological terms it means that a wide range of stimuli become capable, in virtue of some factor

common to all of them, of arousing a stereotyped motor response.

Echolalia prepares the way for, and merges into, the final stage in the development of speech by the child, which is *verbal utterance* – a stage which is itself long and complex and which I cannot now discuss in detail.

The Physiology of Phonetics

Another method of investigating the psychophysiology of speech has sprung from the impetus which the development of electronics has given to communication theory and practice. Electrical methods of recording have made it possible to analyse in great detail the physical characteristics of the sounds of which speech is composed, to synthesize them individually and unite them at will, to vary their physical features, and, in what are known as articulation tests, to investigate the effect of these variations upon the auditory recognition of speech sounds and words. In this growing field of new knowledge I can pick out only a few salient features. The cardinal question is, since the same phoneme, or speech sound, can be produced in an unlimited number of ways, depending upon the pitch of the voice, the resonance of the vocal organs, &c., by what means do we recognize all these variants as identical? This question has proved very difficult to answer. From numerous experiments it has been concluded that 'the listener does not seem to depend upon amplitude alone, nor upon frequency or time alone. The fundamental acoustic determinant of his response is the distribution of energy at different frequencies as a function of time: the intensity-frequency-time pattern' (Licklider & Miller 1951). Liberman *et al.* (1952) artificially produced a single (unvoiced stop) consonant at twelve different frequencies and placed it before each of seven vowels. They demonstrated that the subject might hear the consonant as either k, p, or t, depending on frequency and the vowel by which it was followed, hence what consonant is heard depends not only on the physical stimulus representing the consonant, but also on which vowel follows it, from which they conclude that the following vowel 'plays a critical part in the auditory perception of p and k', and 'in that event the irreducible correlate for p and k is the sound pattern corresponding to the consonant-vowel syllable'. Everyday experience of visual symbols shows the same thing: in reading, the sound which reproduces the letter t is different according to whether it is followed by a vowel or by h.

This leads naturally to the fact that a word is perceived as a whole, which is something different from the mere sum of its parts. This, of course, has long been familiar in all forms of language. It is illustrated by the general principle that in a given time a much larger number of units of speech, whether they be heard phonemes or printed letters, can be recognized if they are presented as words than as nonsense syllables, or as sentences than as isolated words (Egan 1948). Similarly it has been shown that if telegraphists are tested with a strange code or list of figures, they are able to receive only three or four units, compared with forty to sixty in the same time if they are presented with Morse code arranged in words which make sense (Bryan & Harter 1897, 1899). The same thing may be observed in the breakdown of speech in aphasia; for example, a patient with alexia may be able to read an individual word, though he cannot read the letters of which it is composed. All these observations point to the fact that physiologically a word is an organization of a higher order than the units of which it is constructed, and that the organization of these units which follow one another in time actually modifies the perception of the units themselves – an idea closely related to the Gestalt approach of Conrad (1954).

Factors Which Determine Meaning

Just as a word is an organization of a higher order than the phoneme, so a sentence is an organization of a higher order than a word. And like a word, a sentence is an organization, which takes time to come into existence, and in which what happens later modifies the significance of what happens earlier, so that the earlier parts must be held, as it were in suspense, until the later parts determine their meaning. The most obvious example of this is provided by homophones, that is words which sound the same but have different meanings. For example, if I begin a sentence with the words 'The right . . . ', you do not at that stage know what the word 'right' means. I might be going to continue, 'The right way to classify aphasia . . . ', in which case the meaning of 'right' would be 'correct', or, 'The right cerebral hemisphere . . . ', in which case the meaning of the word 'right' would be 'opposite to left'. Thus the meaning of the word 'right' is in a state of suspense until it is determined by words which are heard later. Meaning, therefore, depends upon verbal or syntactical context.

Words derive their meaning also from another kind of context which I propose to call the context of interest – a term which includes attention to an object in the environment or an idea, together with the feelings and intentions of the speaker and hearer with regard to it. Some words obviously have meaning only in relation to the external environment – the word 'that' in 'Give me that', for example, is meaningless unless both speaker and hearer can see what 'that' refers to. But here is a perhaps less obvious example. Consider the five

words: 'Will you take the chair?' What this sentence means can be decided only in relation to the context. It might mean, 'Will you preside at the meeting?' or, 'Will you sit on the only chair in the room?', or, 'Will you remove the chair – with the table?' or, 'Will you accept the professorial appointment?' In the second and third examples the meaning of 'the chair' is determined by the actual physical environment, as well as by the intentions of those present. In the first and fourth instances, the meaning is independent of the physical environment, for the conversation might take place anywhere: it derives from the past experiences, present relationships and future intentions of the speakers. And not only does the context of interest determine the meaning of the word 'chair', but this in turn determines the meaning of the word 'take', which in the four sentences means, preside, or sit on, or remove, or accept. These are psychological facts, but they imply physiological correlates. In other words, at the physiological level, the fact that the context determines the meaning of a word implies that the physiological basis of perception is linked with that of speech when the context is chiefly the external environment. When it is the context of interest – a subjective state – which gives meaning to words, the physiological basis of perception is replaced by those of images, memories, or ideas. The importance of environment in relation to meaning is illustrated in aphasia when a patient succeeds in naming objects in their normal environment which he cannot name if they are presented to him artificially as part of a test.

The Physiology of Speech

We are now in a position to look in more detail at the physiological problems which speech presents. To go back to the beginnings of speech in the infant, we have seen that the child hears what we call *the same sound* produced in many different ways by different people, whereas its own production of this sound is relatively stereotyped. Physiologically, therefore, the first problem is how these widely varying stimuli can produce the same response, that is, by what physiological mechanism the brain responds to a common pattern in the stimuli and disregards the irrelevant elements. To explain this I introduced the concept of the schema (Brain 1950) borrowing it from Head *et al.* (1920), though I use it in a somewhat different sense. The schema, as I use it in connexion with speech, is an unconscious physiological standard of comparison, but unlike the body schema of Head *et al.* most speech schemas, when established, remain stable parts of the permanent equipment of the individual. Thus the physiological basis of the recognition of a phoneme, i.e. of the basic element of speech, is an auditory phoneme-schema. However a phoneme may be uttered, we identify it at once without any process of conscious comparison with a standard: the schema is therefore purely physiological.

We can distinguish two further physiological processes which must play a part in the comprehension of spoken speech. Both are concerned with the meaning of words. That a word exists independently of its meaning is obvious from the facts that a child can learn a word, and adults the words of a foreign language, without knowing what they mean. Their meaning depends, first, on their power to refer to something in the surroundings or to evoke the appropriate ideas. Hence, a word-schema must possess links with the physiological bases of perception and thought. Secondly, the meaning of words depends upon the relationship of each individual word to those which precede or follow it in a sentence, that is upon syntax.

This raises the difficult problem of serial order (Lashley 1951). A sentence is a series of words which follow one another in time, and is subject to laws whereby the meaning of the earlier words may modify or be modified by the later ones. This implies that the physiological activity excited by the earlier word-schemas is a continuing one and also capable of modifying or being modified by later ones. The capacity of the nervous system to hold in suspense a number of linguistic units is well illustrated by the work of telegraphists (Bryan & Harter 1897, 1899). An expert telegraphist, when receiving Morse, does not immediately transcribe what he receives: he prefers to keep from six to twelve words behind the message he is receiving before he begins to transcribe it. The unit of the Morse code is a click, and experiments have shown that such a telegraphist at any moment is storing on the average 237 clicks in their correct time-relationships before he begins to transcribe, and, of course, while he is transcribing those he is receiving a further series. Thus on the receptive side a long succession of stimuli is converted for storage into a persistent or simultaneous state. The reverse happens when an idea is put into words: then we begin with the idea, which exists entire at a specific moment, but finds expression by evoking words in a serial order mutually modified by grammar and syntax. These two factors in meaning, which we may call the syntactical and the semantic, must be very intimately related at the physiological level, because the serial order of words and their syntactical relationships influence their meaning, and, conversely, meaning is reflected in serial order and syntax.

Since I am concerned mainly with principles, I shall not now develop the application of the

concept of the schema to the motor organization of speech, though I shall allude to this when I come back to aphasia.

The Mode of Action of the Schema

By what physiological organization, to take the simplest instance, does an auditory phoneme-schema respond to the common pattern in an indefinitely large range of otherwise dissimilar groupings of phones, that is, sounds? This is only one example of a more general question which is a fundamental one in neurology, namely, the physiological basis of the recognition of patterns, which is an integral part of perceptual recognition. To put the question in another way, how can a large number of variable stimuli elicit the same stereotyped response? Various hypotheses have been put forward in explanation of this, and at the moment they can be no more than hypotheses. If, however, we can formulate a hypothetical principle which will explain the facts, we can then ask the neurophysiologist whether the structure, and the functions, of the nervous system are capable of acting in accordance with the hypothetical principle and whether there is any evidence that they do. If we may regard the schema as a kind of receptor, there cannot be a one-to-one correspondence between the stimulus and the receptor, for in such a case only one particular stimulus would be capable of exciting the response. What we have is a receptor which is capable of detecting, and responding to, *a pattern* in varying stimuli, that is, discovering what set of properties of the stimulus is essential for it to be of a given class. I suggest that most of the features which underlie the recognition of a pattern can be explained at their various stages as the result of *calculating the probability* that a stimulus possesses a certain set of properties.

Regarding speech, consider first the recognition of a phoneme. A large number of phonetic variants, as we have seen, are recognized as the same phoneme. Beyond this range of acceptable phonetic patterns there are others which are recognized only with difficulty, or not at all, or present themselves to consciousness as different phonemes. This can be expressed by saying that for all these variants there is a critical probability which decides whether they are, or are not, identified with the phoneme in question. Fletcher (1953) says that 'articulation values may be considered as probabilities'. The same is true of the reading of handwriting. When we read handwriting which deviates from the normal, what we are doing unconsciously is estimating the probability that a particular pattern represents a particular letter. Beyond a certain point this becomes so improbable that we fail to recognize the letter. There is a critical probability influenced by our memory of previous examples of the handwriting.

Two experts in information theory, MacKay (1956) and Uttley (1956, 1958), have used the probability theory, though in slightly different ways, to explain the capacity of the nervous system to react in a stereotyped fashion to a wide range of varying stimuli. Sholl & Uttley (1953) have proposed a theory of pattern discrimination in which matching consists of an estimate of the probabilities of a collection of variables corresponding to a model built up by previous experience, and they and Sholl (1953) suggest that the organization of neurons in the cortex may fulfil the conditions necessary for this hypothesis to work. Further observations by Sholl (1959) again suggest that the arrangement of cells in the cerebral cortex is such that 'the physiological basis of pattern recognition can only be specified in statistical terms and by probability laws'.

Thus, although we are only at the very beginning of an understanding of these questions, we can see the outlines of a correlation between a psychological and a physiological interpretation of the processes which underlie speech, and that it may be possible to correlate both with the minute structure and functional activity of the cerebral cortex, and we can also see broadly the directions in which we must look for verification of these hypotheses.

The Anatomy of Speech

If we are to escape the mistakes of the naïve psychoanatomists, our aim must be to correlate the physiology of speech with its anatomy, and not try to jump straight from psychological function to anatomical structure. The correlation of the physiology with the anatomy is difficult. We know a good deal about the cortical representation of hearing and vision, and rather less about the cerebral organization underlying the simple movements of speech and writing, for there is still much that is obscure about the physiology of movement in general. Concerning the location of the physiological links between the receptors and effectors in speech, we know very little, chiefly because practically our only information about this is derived from the effects of pathological lesions, and there has hitherto been no adequate physiology in the light of which to interpret them. I shall therefore leave this aspect of the question till my next and final section, in which I discuss aphasia once again. Meanwhile, there are two new aspects of the anatomy and physiology of speech to which I want to draw attention. The only observations on man which can be regarded as using methods in any way equivalent to those of experimental physiology are based upon stimulation of the brain of the conscious patient in the

course of operations, and surgical excisions of localized areas. Penfield & Roberts (1959) have reported that such electrical stimulation may produce either a positive effect – stimulation – or a negative one – interference. The positive effect, which is never more than a cry – vocalization – can be produced by electrical stimulation of the Rolandic and supplementary motor areas of either hemisphere. Stimulation of these areas may also interfere with speech, and interference may be produced by application of the current to the left Broca's and posterior temporo-parietal areas in a right-handed person, and rarely to similar areas of the right hemisphere when that is dominant. Dr J D Spillane has kindly allowed me to mention one of his patients – a man with a left temporal-lobe abscess who had two brief attacks of aphasia while he was having an EEG. In the first he was unable to speak, but could understand what was said to him and this attack coincided with a brief dysrhythmic episode in the left fronto-temporal area. In the second attack he could speak but not understand what was said to him, and the dysrhythmia was in the posterior temporal region. Penfield & Roberts state that the entire supplementary motor area has been excised without permanent aphasia. On the other hand, temporary but sometimes prolonged aphasia may follow removal of the supplementary motor area of the dominant hemisphere. We need more clinical observations on the effects upon speech of lesions on the medial aspects of the hemispheres.

Aphasia has sometimes been observed to result from stereotaxic operations on the globus pallidus or optic thalamus for the relief of parkinsonism. This may be an accidental remote effect, perhaps a disturbance of the circulation in other areas of the brain already recognized as being concerned with speech. There is, however, a possibility that the corpus striatum is more directly concerned in speech than has hitherto been suspected, perhaps through its corticothalamic and thalamocortical connexions. Further observations are needed on this point.

The Physiology and Psychology of Aphasia

To sum up our conclusions so far, we may say that speech employs a series of complex physiological organizations which I have termed schemas, and of which we may recognize in relation to spoken speech (1) auditory phoneme-schemas, (2) central word-schemas, (3) word-meaning schemas, (4) sentence schemas, and (5) motor phoneme-schemas. To serve the purpose of reading and writing, additional visual and graphic schemas are superimposed upon the fundamental schemas of speech, and there is evidence that calculation, musical appreciation and execution, and possibly other skills, have their own independent schematic organizations. If the various schemas enumerated represent individual physiological functions, we should be able to detect in aphasia evidence of their disorganization. But since aphasia is usually the result of a focal anatomical lesion, there will be varieties of aphasia corresponding to disorganization of specific schemas only if each type of speech schema is organized anatomically in isolation from the others, for only then can we expect focal anatomical lesions, if they are not too large, to damage individual physiological organizations.

What type of speech disturbance should we expect to result from a disorder of each particular kind of schema? Since the central word-schema is the basic element in both the comprehension and the expression of words, a disorganization of this will lead to a disturbance of the understanding of words as such, whether they be spoken or written, and also of their phonemic structure and use in expression, again whether spoken or written (i.e. paraphasia and paragraphia). The power of the words to evoke and express meanings will be defective because the words as psychophysiological units are defective.

Word-meaning schemas represent a higher level of physiological organization than central word-schemas. When word-meaning schemas are disorganized the patient will have plenty of words available and will often be able to read and write them correctly, but their power to evoke and express meanings being disturbed, he will not be able to understand much of what he hears and reads, and will have great difficulty in expressing meanings in uttered speech and in writing. This type of disorder may, in milder cases, chiefly affect the nouns, when there is difficulty in thinking of the names of things. In more severe cases when the meaning of verbs and relational words is impaired, speech is more severely affected both in comprehension and expression. When word-sentence schemas are disorganized the patient will show that though he knows the meaning of the individual words, the meaning of the sentence as a whole, created by their syntactical relationships, escapes him.

The aphasic patient is a person with a lesion which, according to its size and situation, is disturbing one or more of the physiological organizations concerned in speech. Only rarely do we find a single type of schema affected alone. In respect of spoken speech, I believe this occurs only with small lesions near the auditory receptor area in the dominant hemisphere, and in relation to the most distal motor functions. The former leads to so-called word-deafness, which physiologically I regard as due to a disorder of auditory phoneme-schemas. The corresponding motor disorder is pure word-dumbness, a disorder of motor

phoneme-schemas, and here the evidence for the association of this symptom with a consistently localized anatomical lesion is much less definite. In either case, it is possible that the degree of damage is more important than its precise localization. Corresponding to these peripheral disorders in spoken speech are pure word-blindness, and the rare disorder, pure motor agraphia in the sphere of reading and writing. Whether one terms all these conditions varieties of aphasia or varieties of agnosia and apraxia is, I think, purely a matter of definition.

When we come to the effect of brain lesions upon central word-schemas, word-meaning schemas and sentence-schemas, the situation becomes extremely complex, and will require more work for its elucidation. There are two reasons for this. Since all the evidence indicates that the anatomical basis of these physiological functions is situated in a comparatively limited area of the temporal lobe and the adjacent parietal lobe in the dominant hemisphere, and since the lesions which produce aphasia tend to be large, every possible degree of disorder of these specific functions may exist in combination, not only with each other but also with pure word-deafness. The second reason is that disorders of different physiological functions may produce similar psychological defects. Thus, if there is a disorder of central word-schemas, since the accurate use of words is essential to syntax, syntax will also be disturbed, but so it will too if the central word-schemas are intact but their ability to elicit meanings is disordered, or again if the syntactical use of words, that is, their serial order and resulting modifications, is disorganized. Owing to the complex functional interrelationships between the different types of schema, then, we cannot directly correlate what we describe as a single psychological disorder, such as defective syntax, with a single kind of physiological breakdown, as Bay (1957*c*) has pointed out. Schuell (1950) makes the same point in relation to paraphasia, which, he says, is not simple or single in ætiology but may indicate a breakdown at various 'pre-speech' levels. He attributes it to an 'imperfect control of the motor by the sensory mechanism, if sensory mechanism is understood to include the mechanisms of integration as well as reception'. Exceptionally we can recognize in pure or relatively pure form a disorder of auditory phoneme-schemas, pure word-deafness, of central word-schemas, which I have called central aphasia, or of word-meaning schemas, which in my view includes nominal and amnesic aphasia. Much commoner must be a combination of word-deafness with central aphasia, of central aphasia with nominal aphasia, or of all three, and I suspect that severe jargon aphasia, in which the patient's thought is so disturbed that he fails to recognize his disability, is the product of a combination of a severe form of central and nominal aphasia. On the expressive side again we meet with a pure form in pure word-dumbness, or apraxic anarthria due to loss of motor word-schemas.

The nature of Broca's aphasia is still uncertain. I think it represents the breakdown of a physiological organization intervening between central word-schemas and motor phoneme-schemas, but combinations of Broca's aphasia with apraxic anarthria or central aphasia, or both, must be common.

Here we return to our starting point. What I have just said shows how impossible it is to infer from cases of aphasia the physiological organizations underlying speech. It also shows the inadequacy of purely psychological classifications of aphasia, and still more of the attempt to correlate disturbances which can be classified psychologically with lesions in particular situations. We have seen that the physiological organizations upon which speech depends are of great complexity, extend over considerable areas of the brain, and are organized in time as well as in space. These serve psychological functions, but the breakdown of a physiological schema does not necessarily or indeed usually disturb speech in a way that corresponds to a single type of psychological defect. Moreover, the anatomical organization of the schema means that only rarely will a single type of schema be disturbed in isolation from others. Hence what the clinician calls aphasia is almost always the product of a mixture of physiological disturbances resulting in a complex medley of psychological disabilities. For the present, therefore, the classification of the aphasias must be largely empirical. The task of the future is to use all the available modern methods of psychological testing, linguistics, phonetics, and communication theory, to correlate psychological with physiological functions. Already we can see the directions in which progress is likely to be made. Stanton (1958) has shown that 'delayed auditory feedback' may throw light on the disorder of function in aphasia at the sensorimotor level. Alajouanine & Mozziconacci (1948), Alajouanine (1956) and Bay (1957*a*, *b*, *c*, *d*, 1960) have studied phonetic disintegration, and Bay has also investigated the relation between aphasia and other types of psychological disorder. Schuell's work has already been mentioned. Probability theory has been applied to normal speech (Miller 1951, Licklider & Miller 1951, Fletcher 1953), and Herdan (1958) has applied it to aphasia in a statistical study of the vocabulary of aphasics. By such investigations we may hope to arrive at an analysis of speech disturbances at both the psychological and physiological levels,

and of their interrelationships, which will provide a scientific basis for the recognition of the types of disorder of function present in each individual aphasic patient.

Acknowledgment: I am grateful to Dr A M Uttley for his helpful comments.

REFERENCES

Alajouanine T (1956) *Brain* **79**, 1
Alajouanine T & Mozziconacci P (1948) L'Aphasie et la désintégration fonctionnelle du langage. Paris
Bastian H C
(1898) A Treatise on Aphasia and other Speech Defects. London
Bay E
(1957*a*) *Dtsch. Z. Nervenheilk.* **176**, 553
(1957*b*) *Dtsch. Z. Nervenheilk.* **177**, 1
(1957*c*) *Psychiat. Neurol. Basel* **134**, 298
(1957*d*) *Nervenarzt* **28**, 450
(1960) *Nervenarzt* **31**, 145
Black J W (1951) *J. Speech Dis.* **16**, 56
Brain W R (1950) In: Perspectives in Neuropsychiatry. Ed. D Richter. London; p 127
Broca P (1861) *Bull. Soc. Anthrop. Paris* **2**, 235
Brown R W (1956) In: A Study of Thinking. Ed. J S Bruner *et al.* New York; appendix
Bryan W L & Harter N
(1897) *Psychol. Rev.* **4**, 27
(1899) *Psychol. Rev.* **6**, 345
Bühler K (1930) The Mental Development of the Child. London
Charcot J-M (1887) Leçons sur les Maladies du Système Nerveux. Paris; **3**, 187
Conrad K (1954) *Brain* **77**, 491
Egan J P (1948) *Laryngoscope, St Louis* **58**, 955
Eisenson J (1938) The Psychology of Speech. London
Fletcher H (1953) Speech and Hearing in Communication. New York; p 280
Froment J (1935) In: Traité de Physiologie Normale et Pathologique. Ed. G-H Roger & L Binet. Paris; **10**, 1229
Goldstein K
(1948) Language and Language Disturbances. New York. p 50
Head H
(1926) Aphasia and Kindred Disorders of Speech. Cambridge
Head H *et al.* (1920) Studies in Neurology. London; **2**, 605
Henschen S E
(1920) Klinische und anatomische Beiträge zur Pathologie des Gehirns. Stockholm; Pts 5 and 6
(1922) Klinische und anatomische Beiträge zur Pathologie des Gehirns. Stockholm; Pt 7
Herdan G (1958) *Confin. Psychiat.* **1**, 143
Jackson J H
(1861) *Med. Times Gaz.* **1**, 196
(1878) *Brain* **1**, 304 (reprinted in *Brain*, 1915, **38**, 107 and in Selected Writings of John Hughlings Jackson, 1932, London, **2**, 155)
Kleist K (1959) Sensorische Aphasie und Amusien auf Myeloarchitektonische Grundlage. Stuttgart
Lashley K S (1951) In: Cerebral Mechanisms in Behavior. Ed. L A Jeffress. New York; p 112
Lee B S (1950) *J. acoust. Soc. Amer.* **22**, 824
Liberman A M, Delattre P & Cooper F S
(1952) *Amer. J. Psychol.* **65**, 497
Licklider J C R & Miller G A (1951) In: Handbook of Experimental Psychology. Ed. S S Stevens. New York; p 1068
MacKay D M (1956) *Brit. J. Psychol.* **47**, 30
Miller G A (1951) In: Handbook of Experimental Psychology. Ed. S S Stevens. New York; p 989
Penfield W G & Roberts L (1959) Speech and Brain-mechanisms. Princeton & London
Schuell H (1950) *J. Speech Dis.* **15**, 291
Sholl D A
(1953) *J. Anat., Lond.* **87**, 387
(1959) *J. Anat., Lond.* **93**, 143
Sholl D A & Uttley A M (1953) *Nature, Lond.* **171**, 387
Stanton J B (1958) *Scot. med. J.* **3**, 378
Uttley A M
(1956) Proc. I Int. Congr. Cybernetics, Namur. Paris; p 830
(1958) In: Mechanisation of Thought Processes. Nat. Phys. Lab. Symposium No. 10. London; **1**, 119

Meeting February 2 1961
at the West End Hospital for
Neurology & Neurosurgery London

The following cases were shown:

Radiosensitive Tumour of Body of Third Dorsal Vertebra ? Solitary Beta Type Myeloma
Dr N G Hulbert

Myelomatosis Destroying Third Cervical Vertebra, Treated by an Acrylic Inlay
Mr G C Knight

(1) Right Occiptal Cirsoid Aneurysm and Intracranial Angioma Treated by Ligation
(2) Carcinomatous Neuropathy
Dr T Rowland Hill

Meningovascular Syphilis
Dr E H Jellinek (for Dr R E Kelly)

Familial Muscle-wasting of Peripheral Distribution with External Ophthalmoplegia
Dr J A R Tibbles (for Dr Gerald Parsons-Smith)

High Brain-stem Encephalitis Responding to E.C.T
Dr Gerald Parsons-Smith

An Intermittent Brain-stem Syndrome
Dr E Gilchrist (for Dr T Rowland Hill)

A Brain-stem Disturbance
Dr J N Milnes

A demonstration was given of **Stereotactic and Ultrasonic Techniques**

Books recently presented and placed in the Society's library

Hawker L E et al
An introduction to the biology of micro-organisms
pp 452 35s
London: Arnold 1960

Herxheimer H
Grundriss der Sportmedizin für Ärtze und Studierende
pp 192
Leipzig: Thieme 1933

Hewitt Sir F W
Anaesthetics and their administration
4th ed pp 676
London: Macmillan 1912

Hewlett R T
A manual of bacteriology: clinical and applied
3rd ed pp 638
London: Churchill 1908

Hewlett R T
Pathology: general and special for students of medicine
2nd ed pp 585
London: Churchill 1907

Holstein M H
Biology of *Anopheles gambiæ*: research in French West Africa
pp 172
Geneva: World Health Organization 1954

Hunter D
Health in industry
pp 288
Harmondsworth: Penguin 1959

Italy. Congresso Nazionale sulle Malattie della tiroide
Le tireopatie. Vols 2–6
Torino: Checchini 1958

Jennings H S
Genetics
pp 351
London: Faber 1935

Johnson W H
Oral radiography
pp 145 42s
London: Ilford & Heineman 1959

Jopling W H
The treatment of tropical diseases
pp 202 20s
Bristol: Wright 1960

Jopling W H
Differential diagnosis for practitioners in the tropics: a clinical handbook
(in collaboration with Sir Philip Manson-Bahr)
pp 159
Leverkusen: Farbenfabriken Bayer AG 1959

Kettle E H
The pathology of tumours
pp 224
London: Lewis 1916

Kiss F & Szentágothal J eds
Atlas of human anatomy
8th ed 3 vols
Budapest: Hungarian Academy of Sciences 1960

Kyle H M
The biology of fishes
pp 396
London: Sidgwick & Jackson 1926

Lewis Sir T
Clinical science: illustrated by personal experiences
pp 189
London: Shaw 1934

Lewis Sir T
Research in medicine and other addresses
pp 75
London: Lewis 1939

Lewis Sir T
Pain
pp 192
New York: Macmillan 1942

Lewis Sir T
Vascular disorders of the limbs
2nd ed pp 118
London: Macmillan 1949

Lob A
Die Wirbelsäulen-Verletzungen und ihre Ausheilung
2te Aufl pp 272 DM 78
Stuttgart: Thieme 1954

Section of General Practice

President L W Batten MRCP

Meeting March 15 1961

Discussion on General Practice in a Changing World

Dr John H Hunt (*London*)

I have worked in neither the U.S.A. nor Canada. My experience of general practice is limited to the United Kingdom and Eire, a short trip a few years ago to see general-practitioner clinics in Scandinavia, a small experience of general practice in India between the two world wars, a trip to Russia for five weeks last summer, and a recent six-week journey to New Zealand and Australia. On the way there my 'plane was delayed in Fiji for a few hours; the airport doctor gave me the names of three general practitioners on the island who showed me their surgeries, their homes, and their patients.

Air travel has made journeys to these distant places comparatively easy. My grandmother took six months to reach New Zealand from London on her honeymoon in the 1870s; I did the same journey in just under twenty-four hours flying time. The medical services in many of these countries are developing so quickly, and in so many different ways from our own, that I feel sure we should learn a great deal from them. Sometimes I wonder whether it would not be worth while to appoint official 'medical attachés' to some of them so that our Ministry of Health or its advisers could keep in close touch with what they are doing.

The role of the general practitioner: Eleven years ago, on the day the Collings' Report was published – March 25 1950 – the leading article in the *Lancet* (1950) said 'We have to decide what the general practitioner should be doing, and then – whatever it is – enable him to do it properly'. The significant words are, of course, 'whatever it is'. Until we know just what he should be doing, we cannot tell how many doctors we need, how they should be trained, what equipment and premises they require, or how they should work.

Almost exactly a year ago, Dr Fox (1960) put the cat among the pigeons by writing in the *Lancet* that 'general practice is dead or dying in this country' and that elsewhere 'except in isolated places the general practitioner is already extinct'. That is one way of solving the problem – to wipe the slate clean and start afresh – but there happen to be about a quarter of a million general practitioners in the world who really believe they *do* exist, and somehow we must determine their role and their duties.

The titles 'general practice' and 'general practitioner': It is worth considering whether the title 'general practice' is really correct; if not we should try to change it, however troublesome this might be. We are certainly in 'practice' – I do not think anyone could doubt that; the main question is, are we still 'general' in spite of being no longer comprehensive? We can get some help in this, I think, by considering a general store. No general store anywhere in the world – from a small one in Texas to a large one like Harrods in London – can possibly sell *everything*. The fact that one cannot go into Harrods and come away easily with a brick, a bumble bee, a blunderbuss, a baby or a bulldozer, does not, I think, prevent that store from considering itself to be 'general'; and the work of a doctor, even if he is not doing heart surgery, complicated biochemistry or radiotherapy, can still, I believe, be described as 'general' so long as his outlook is broad and his interests are widespread.

We should consider carefully the suggestion which Dr Fox made last year that we should replace the title 'general practitioner' by 'personal doctor'. In some ways it is a good idea and one worth examining carefully. Before discussing this point I would like to make quite clear that no one believes more strongly than I do in a close and happy doctor/patient relationship, in the importance of the psychological aspects of our work, and in the 'art of medicine'; all of which I put first in my Lloyd Roberts Lecture four years ago (Hunt 1957). It seems a pity to limit the word 'personal' to our work alone, because this implies that the work of specialists is impersonal which is often not the case. I believe that all good

doctoring – by general practitioners and by specialists–must be personal; no one's work could be more personal than that of some psychiatrists and gynaecologists. In the past certain eminent people have, quite rightly and properly, taken a doctor with them on their travels round the world – one doctor for one patient – which is my idea of a truly 'personal doctor'; the adjective being used here in the same way as in 'personal maid'.

The term 'general practice' is now so firmly established, and so many institutions have adopted it in their titles (The Section of General Practice of the Royal Society of Medicine is but one example), that I do not believe this is the time to consider a new international nomenclature unless there is overwhelming argument in its favour. I, myself, would be as sorry to see us called here 'The Section of Personal Doctoring of the Royal Society of Medicine', as I would be sorry to see the familiar initials G.P. replaced by P.D.

Different types of general practice: There are, of course, all kinds of general practice – family doctoring, school doctoring, factory, ship and service doctoring and so on – and the varieties of each can be multiplied indefinitely. No two civilian practices are the same. In New Zealand, in the forests at the tip of the South Island, where a great deal of logging goes on, a doctor in practice amongst the sawmills told me that it was exceptional for him to see an adult male who still had a thumb and all four fingers on each hand. The flying doctors with whom I flew in Tasmania and Australia do all the ordinary work of general practitioners, except that they travel by air instead of by car. Some of their patients live 400 miles from the nearest doctor or chemist, and are only connected with them by rough tracks crossing unbridged rivers. One can imagine what it must have been like to have fractured one's femur under those conditions, or to have developed a perforated appendix or duodenal ulcer, before the flying doctor service brought to these people what has been so aptly called a 'mantle of safety' – giving them a sense of security, and freedom from isolation and fear, for which they are extremely grateful.

The point I wish to make is that no one in any country can generalize too much about general practice. I have made the plea before, and I would like to make it again – that every Health Service should be kept flexible and be looked upon as a long-term experiment so that it can develop and evolve when others have something to teach it. The danger, when any service becomes too highly organized, is that evolution cannot easily take place. Our National Health Service was planned, sums of money were set aside and rules and regulations were made, before we really knew what general practitioners should be doing. When we have decided this, great changes may be needed. The whole world is watching us, and it will be interesting to see how many other countries copy us.

General-practitioner centres: I was impressed by Dr Fox's suggestion that we should encourage in this country the development of general-practitioner posts (Fox 1960). I am sure he is right. In the reforming zeal after the Second World War, it was thought that health centres might provide these for us, but on the whole they have been disappointing. Dr Guy Ollerenshaw and I wrote a paper seven years ago (Ollerenshaw & Hunt 1954) suggesting such centres, away from main hospitals, which we called 'Family Medical Centres'. We thought that they should have whatever the general practitioners in the district wanted – a common-room for doctors to meet and have coffee or tea (or even a buffet lunch) and in which to talk to local-authority and social workers, a small library, a room for dressings and other nursing care (perhaps with a nurse in charge), a minor operating theatre, a pathological laboratory, an X-ray apparatus, or perhaps an electrocardiograph. I must stress that every such general-practitioner centre will be different, depending on the number of doctors using it (from 5 to 50 or more) and what is needed in that particular area. We are watching with great interest the centre that has recently been opened at Peckham – the South East London General Practitioner Centre (serving about 80 family doctors) – and the one being built as an annexe to the new Charing Cross Hospital. Neither may be a complete success; but we are certain to learn something from them and they are steps in the right direction.

Ancillary services: We have now many ancillary services for general practitioners in our cities; some doctors may have ten or more different helpers – receptionists, secretaries, surgery nurses, district nurses, midwives, health visitors, psychiatric social workers, almoners, maternity, child welfare and school health workers, dieticians, physiotherapists, rehabilitation and occupational therapists–and I am just a little afraid of the dangers inherent in having too large a health team. We must recognize that many people prefer a single doctor friend to a panel of medical advisers and acquaintances, and I do not believe that a committee can ever replace a good family doctor. If there are too many members of the team, they are liable to work independently, perhaps giving differing or contradictory advice. If they work too closely together, an extra psychologist may be

needed, as Dr Silver (1960) has hinted, to sort out the interpersonal relationships between different members of the team.

General-practitioner beds in hospitals: It is important, I believe, that general-practitioner beds in hospitals should be in general-practitioner hospitals or in general-practitioner annexes of general hospitals, rather than inside the general hospitals themselves. Some people say that family doctors in this country are so busy that they do not need hospital beds; but I have never been really convinced that a patient with a general-practitioner complaint – a boil on his leg, a sprained ankle, or lumbago – when he has to go into a hospital bed just because there is no one to care for him at home, always needs to be cared for in that bed by a specialist. I can see no logic in the argument that while such a patient is upright he can well be looked after by his family doctor, but as soon as he lies down he becomes a case for specialist care. On average each general practitioner in England and Wales has charge of less than one-half of one hospital bed, which is not enough. In Canada, the United States, New Zealand and Australia, the majority of general practitioners can put some of their patients into hospital beds and look after them there. They feel fairly treated, they are in close touch with specialists, and my impression is that their clinical enthusiasm is greater on the whole than it is in many family doctors in our country.

General practitioners with special interests: There are not enough specialists to go round, so that many general practitioners must do a certain amount of special work whether they like it or not. There are more than 40 different specialties, with some of which family doctors have little in common; but some concern them greatly – internal medicine, obstetrics, pædiatrics, geriatrics, psychological medicine, minor surgery and accident work, and public health. Doctors with these special interests must not become too involved in them; they must remain primarily good general family practitioners. The last thing we want is a great number of low-grade specialists. In Russia there had been, I found, a tendency towards this: when I asked why some of the doctors visiting patients in their homes had no knee-jerk hammers, or instruments for looking inside the ears or eyes, I was told that they referred all those cases to the polyclinic specialists. But a number of Russian doctors had already revolted against this, and many were, in fact, carrying these instruments because they could not tell whether there was anything wrong with the ears, or nose, or nervous system of their patients until they had tested them.

General practitioners and specialists: The work of general practitioners and specialists must be complementary. Good medicine is impossible if family doctors are isolated from specialists for too long – it is good for both to keep in close touch, speak the same language and to rub shoulders with each other. The present wide gap between the two *must* be narrowed. There is a need, too, for a stepping stone from general practice to specialism. Some general practitioners who find that they become particularly interested in a speciality may want to take it up altogether; conversely, some young specialists may find that after all they prefer general practice and may wish to come back into the fold.

It is an interesting fact that the more a general practitioner knows about a special subject, the more likely he is to call in the help of a specialist in that subject when he does find something wrong. The advent of general practitioners with special interests increases, I believe, rather than diminishes the work of the specialists in a district.

I suspect that there is far more general practice going on in the United States than Dr Silver (1960) suggests, carried out largely perhaps under the cloak of a specialty because specialists can command higher fees. There is an aura about the word 'specialist' which has, I believe, reached its peak and is now declining. In New Zealand I was told of a group of six doctors who were working happily together until one of them put 'pædiatrician' after his name on his plate, another put 'dermatologist' and another one 'surgeon'. An Irishman, a member of the group, not to be outdone, put after his name just the word 'specialist'. His colleagues were bewildered and asked him in what he specialized. 'In caring for my patients' he said, and he had the largest practice of them all!

'*Rotten*' *doctors:* If anyone tells me that some general practitioners in his area are 'rotten doctors' who do not examine their patients or take proper histories, or write good letters, I always ask 'who selected these peculiar men and women to be medical students, who taught them, and who decided the conditions under which they should work?' If the general practitioners in any area are really bad it is a serious indictment of their selection, their training, or the conditions under which they have to work. In the training of family doctors of the future general practitioners will almost certainly have to play an increasing part in student-selection, student-attachment, as general-practitioner advisers to teaching hospitals, in departments of general practice, in general-practice teaching units, and even in chairs of general practice in the universities which I believe will come in time.

'Erosion' of general practice: I do not agree with the suggestion which is so often made that general practice is being 'eroded' by the work of the specialists and that family doctors are now working only with 'what is left over' as 'residual legatees'. I feel that the scope of general practice has increased enormously during the past few years, and so much that is well worth while has been added to it, that drastic pruning is now necessary – to cut out everything which other people can do better than we can, so that we may concentrate on what we can do better than any specialist or hospital. We should not be ashamed of not doing renal biopsies, cardiac catheterization, or lung resections; we should be only too thankful that there are people who will carry out these techniques for us, giving us time for the work which we alone can do really well.

It is sometimes suggested that general practitioners wish to return to their pre-eminent position in the medical services. I do not believe that this is so. Medicine is so complicated now, there are so many specialists and the team is such a huge one, that I do not think any members of this team should be pre-eminent.

The size of the problem: In our country we still have a great many problems connected with general practice. Multiply these by the number of countries in the world and one begins to realize what Sir Robert Platt (1957) meant when he said a few years ago that 'the exciting days of general practice are only just beginning'.

There is a shortage of doctors throughout the world. There is also a shortage of food – we are told that about half the population of the world is living on less than 1,600 calories a day – and every country is short of money for its medical needs. In Tibet there are only a few qualified doctors; in Ethiopia there is one midwife to a million people; in parts of Central Africa there is only one doctor to about 200,000 people. Like all these we, too, have to improvise and make the best of what we have got.

Financing the general-practitioner service: No country could afford the fullest general practitioner service financed by its treasury alone – the cost would be astronomical. Even the Russians have realized that their medical service cannot give everyone all the care and attention that is sometimes needed; there is now private practice in the U.S.S.R., and the State has built private medical and dental clinics. Every country must decide what proportion of its income it can spend on a national family-doctor service, and whether or not it will allow patients to pay for additional benefits through personal insurance or private fees.

In New Zealand and Australia a patient can receive from the *same* doctor his state-financed and privately-financed general-practitioner care. In our country he has to go to a *second* doctor for everything which the National Health Service cannot afford to provide. Other countries feel that we have made a mistake in splitting our general practice like this, and that it gives rise to many unnecessary difficulties and frustrations; it is one of the main reasons why they do not wish to copy us.

To change just now might prove difficult. But if a method could sometime be found of integrating and overlapping satisfactorily, in the work of a single doctor and in a way which could not easily be abused, all the family-doctor services of a patient, however they are financed, I believe that this would help many patients, it would restore to many doctors incentive and encouragement to improve their work, and it would pay for better general practice in Great Britain.

The need for good general practice: Nearly everyone seems to agree that good general practice is still essential for any good medical service. The editorial in the *Lancet* of March 4, 1961, said 'the most important problem in medicine today – that of providing in all countries enough doctors well trained for family practice'. There is an urgent need everywhere now to fit general practice into the framework of modern medicine. Rather than deny its existence, or change its name, our job is to train more students properly in this branch of our profession and to raise its standard and its status so that anyone will be proud to join it. Collectively, our responsibility in this is to the Commonwealth, if not to the whole world; we have a unique opportunity now to give a lead to other countries and to set them an example. Individually, the personal responsibility of each one of us is the welfare of his own patients in and near their homes. It is not only the flying doctor's patients who appreciate the mantle of safety, comfort and guidance which a good family doctor can spread over them: most other people appreciate it too, even in the largest cities. May the lives and work of all of us reflect the spirit of Albert Schweitzer's simple words written on the beacon of his wharf at Lambaréné in West Africa: 'Here, at whatever hour you come, you will find light and help and human kindness.'

REFERENCES

Fox T F (1960) *Lancet* i, 743
Hunt J H (1957) *Brit. med. J.* i, 1075
Lancet (1950) i, 549
(1961) i, 491
Ollerenshaw J G & Hunt J H (1954) *Med. World* 80, 509
Platt R (1957) *Brit. med. J.* ii, 1236
Silver G A (1960) *Med. World* 92, 55

Dr T F Fox (*London*)

One of the great changes in our world is that big enterprises are taking the place of small ones. Our wants are no longer supplied by people near at hand – the miller, the blacksmith, the tailor, or the poulterer. Instead our flour is processed in a distant factory; the spare parts of our car come from the works; clothes of every size can be bought 'off the peg'; and a vast biological factory supplies us with broilers ready for the pot. In the same way the technical revolution is substituting the supermarket for the little man round the corner; and in medicine, unless we call a halt, it may substitute the hospital for the individual practitioner.

In Britain general practice has been temporarily preserved by the National Health Service. Some may think the preservation has been done at the cost of putting practice in a deep freeze; but at least the general practitioner's independent status has been maintained for the time being. With this respite we have a chance to consider whether in future a general practitioner, outside the hospital service, will be really needed; and if so, what he should do. In a closely packed society, with good transport and telephones, do people still require their own doctor round the corner? Or should they change their habits and get all their medical care from the hospital?

My recent thoughts about this I owe largely to Dr Silver. He thinks that – anyhow in cities – independent practitioners are obsolescent; and that a group of specialists, based on the hospital, should take their place. But he recognizes that the passing of the old-time family doctor may leave a real gap. Hence his group at the Montefiore Hospital in New York not only provides first-class specialist care but also tries to give each patient the security and comfort of having a doctor whom he can regard as his own.

In the U.S.A. specialization and mass-production are widely accepted as synonymous with progress, and my own impression from seeing the Montefiore and other examples of group care was that before very long the American public in cities may be content to get all medical care from groups based on hospitals. Moreover I think that such groups can do everything better than the independent practitioner – everything except one. The exception is this. By its very nature a group cannot give the best kind of *personal* medical care.

Not only the Americans but we too have to decide how much this matters. And our answer, I think, will depend on our concept of medicine – on whether we believe that the doctor exists to look after people or to look after diseases. These are two opposing schools of thought, and we shall make little headway till we decide which school we belong to.

A great many people hold that the acid test of a medical service is simply this: does it pick up the serious diseases in time, so that they can have efficient treatment? To such people the centre of gravity – the heart – of medicine is in the hospital, where the efficient treatment of serious disease is usually decided upon or given. In their eyes the outside practitioner is doing his job if he ensures that any disease needing active treatment is spotted quickly and referred to the specialist; and it does not really matter if his management of minor illness and anxiety appears perfunctory. After all, the large majority of disorders cure themselves whatever is or is not done for them.

I suspect that not only many specialists but also many general practitioners see practice like this, and that their opinion on what is good now and desirable for the future is based on their belief – conscious or unconscious – that hospitals are the temples of medicine.

This is the idea we got when we were students, and it is far from unreasonable. But if that is what we think, do we accept the corollary? The plain fact is that, with distances shortening, we cannot go on claiming autonomy for the private practitioner if his function is only to be a sorter of diseases. Important though this function is, it could be performed at least as well, and very likely better, by a group of specialists at the local hospital.

To justify the independent practitioner we have to accept, at any rate partly, the opposite concept of medicine, that it consists in the continuous care of *people*. On this view the need for diagnosing and treating disease properly is in no way less; but the hospital is auxiliary to the practitioner, not the practitioner to the hospital.

As I see it, this second concept of medicine is the right one. In practice it is clear that as the specialties have got cleverer and more diverse, the patient has more (not less) need of a wise doctor who will look after him as a person – in relation to his family, his work, and his other circumstances. Everybody needs a medical friend who will help him to get the best out of his life by avoiding illness, by overcoming it, or by putting up with it – an experienced adviser who will sometimes send him to a specialist but sometimes stop him going to one. This kind of judicious care over the years is one of the things that people not

only want but really need; and they can get it best from someone who lives near them and knows their home. I do not see how any member of a hospital group – however benevolent and however well organized – is going to have the same sense of personal responsibility as an independent doctor who agrees to take medical charge of someone through the years.

If we want the independent general practitioner to survive, then, he must concentrate on the only work that cannot be done equally well by the hospital. He must become above all, a *personal* doctor. And if this were really accepted, it would mean, I believe, a gradual change in our idea of general practice. I do not expect the general practitioner to change his name: that would be asking too much. But I do think we ought to change our criteria – our basis for judging success. To-day a practice may still be classed as good if it is an efficient sorting agent which picks out all important remediable disease and sends it to the specialist. But if we look at the practitioner as a personal doctor, such a practice may be gravely defective. The personal doctor has to do much more than sort; and he cannot do it well unless he really knows his patients and listens to their troubles. In our profession some people think that all the time a patient really needs – all the time to which he is medically entitled – is the time required for discovering whether he has something seriously wrong: anything more than that is 'frills' – a luxury which he cannot reasonably expect unless he comes as a private patient. But this misconceives the essential function of the independent practitioner, which is to look after the patient as a person.

In talking about the personal doctor, I am very far from proposing a lower professional status. A friend of mine accused me of wanting to turn the practitioner into 'a sort of medical curate; one who visits, exchanges ideas, throws out suggestions, but, in fact, accomplishes precisely nothing of therapeutic value'. On the contrary, I want him, in taking full charge of people, to assume considerably more responsibility than most practitioners assume to-day; and to justify this responsibility he must have clinical skill and self-reliance. If the practitioner is to fulfil his purpose, he must feel that he himself – not some anonymous group in a hospital – is the patient's own doctor; and he will never feel this unless he makes his own diagnoses as fully as his facilities and time allow. Also his judgment, in relation to that of the specialists, will not carry much weight unless he has a pretty good knowledge of medicine.

And here I come to what looks like a paradox. Though I am saying that we should resist absorption of general practice by the hospital service, I do not see how the personal doctor can keep up to date and do his work really well unless he draws closer to the hospital. Though the personal doctor, as such, should have full professional independence, being subordinate to no other person or institution, he is likely to be much better at his job, and more interested in it, if he is always in and out of hospital, talking to the specialists there about his cases.

The contact of practitioner and hospital should, I suggest, be of two distinct kinds:
(1) All outside doctors who are prepared to co-operate by sending the specialists decent notes should be made associate members of the staff of the hospitals where they work. They would have free access to any of their patients who are admitted, and on such visits their comments and help would be regularly invited. They should be welcomed, too, on any ward round; they should have use of the library; and there should be at least one comfortable room which they could regard as their home in the hospital and where they could meet their specialist colleagues.

(2) Quite apart from his associate membership of the hospital staff, a man who is in personal independent practice should be able, if he wishes, to spend part of his time working in a specialist service, either in the hospital or elsewhere. But only on one condition. The personal doctor who wants to practise any specialty must, for that purpose, join the appropriate specialist team. As personal doctor he is an independent practitioner, professionally the monarch of all he surveys; but in so far as he decides to be also a specialist, part-time, he must accept the leadership of a whole-time specialist at the hospital. Many will disagree with me, but I believe those are the only terms on which, in the National Health Service, a general practitioner should undertake obstetrics, and the only terms on which he should admit patients into general-practitioner beds. When he undertakes work for which the hospital service is ultimately responsible, he must do so as a member of the hospital team.

In the same way those practitioners who are more interested in public-health and social work than in that of hospitals may prefer to attach themselves to the staff of the M.O.H. or of the local industrial health service.

Whether or not they take a special interest in public health, all personal doctors should of course have links with the M.O.H.'s department, which can lend them the ancillaries and the equipment often necessary for home care. And I agree, of course, that the practitioner is the fitting leader

for what may be quite a large team looking after his patient in the home. At the same time, personal practice is not something that can be deputed to other people under the doctor's distant supervision; and what looks like a logical piece of organization may, by becoming too big, defeat the sole object of having a personal doctor – by making him impersonal.

To the public the ideal doctor is a man on duty, accessible and fresh, day or night, for a lifetime. To the doctor the ideal practice is one which gives him a chance to relax, and read and take exercise, and be civilized, and even mix with his family. Passionately though I am propounding the doctrine of the personal doctor who is really personal, I would agree that partnerships of two or three practitioners are usually desirable as well for the body as for the soul – to preserve the doctor's health and to give him everyday professional support and companionship, beyond what he can get by visiting the hospital and talking to specialists. On the other hand, if personal practice is really our aim we should beware of the larger group with its complex organization and its impersonal building resembling a minor hospital. In this country, where real specialists can be found so close at hand in hospital, there will surely be less and less need for the kind of group whose members confine themselves mainly to particular specialties. And in so far as health centres were to be a sort of half-way house between personal practice and the hospital, the decision not to develop them was wiser, perhaps, than some of us thought at the time.

In brief, then, my argument is that only as a personal doctor is the independent general practitioner likely to survive. At present his independence is protected by the N.H.S., but this is only a reprieve; for a time may well come when people will say 'The hospital is the best place for modern medicine; so let's get all our care there'. I do not myself believe that any hospital group can give continuous personal care of the kind given by the best practitioners to-day: and, if that is so, to replace the independent doctor by a hospital-based service would be to choose a second-best.

But if the general practitioner is to regain his position as the patient's real doctor, he must be able to offer more than he usually offers to-day. Not only must he have a vocation for doctoring but also he must have equipment and time for doing first-rate work. He will hardly regain his responsibility and his autonomy unless he is as good at his own job as the specialists are at theirs – unless he collaborates with them on equal terms. If these conditions for personal practice are never going to be realized, he may as well abandon the struggle for independence and join the hospital group.

In asking that doctors should give their patients more time and thought, one is also asking for more doctors – which we may never be able to get. But even if we cannot afford the best, we ought to know what it is. My own idea of the best is to have the medical supermarket, by all means, but *also* the man round the corner.

Dr George A Silver (*New York, U.S.A.*)

Planning for Family Medical Service

You have had in this country several serious analyses of general practice such as those of Collings (1950) and Taylor (1954), periodic observations such as those of Logan (1960) and Backett (1960) and even presentations in the lay press on the present state and future possibilities of general practice. Dr Fox (1960) put the argument into perspective by entitling his paper 'The Personal Doctor'. The problem is really one of providing an adequately trained and interested family doctor. Serious thought must be given to the implementation of the ideals of family practice partly because of the decline of general practice, partly because of the rise of specialism and partly because of the increasing need for family advice and guidance under the pressures of changing social situations and changing medical knowledge.

In the United States, the declining role of the general practitioner and the corresponding increasing importance of specialism has been more rapid and more readily visible than in England. The American Medical Directory for 1958 notes 39% general practitioners, 14% partial specialists and 47% full specialists. In 1950, 48% of practising physicians were general practitioners, 15% partial specialists and 37% full specialists. That this trend is unrelenting is evidenced by Weiskotten's periodic reviews of trends in specialization, the latest of which shows 68% of the 1950 graduating class in speciality practice (Weiskotten *et al.* 1960).

Another element of change in the response to increasing complexity and depth of knowledge of modern medicine is the development of partnerships and group practice arrangements. Group practice growth parallels the growth in specialism. It is clearly an effort to restore unity from the fragmentation of practice which specialism induces.

Means (1953) writes: 'The time has come, because of the complexities of modern diagnosis and treatment, when medicine should be practised usually by groups of doctors rather than by individual practitioners, . . . Without such organization, in one form or another, full advantage of our rapidly expanding scientific knowledge cannot be taken for the benefit of patients.'

In 1946 (when the first survey of group practice in the United States was made) there were less than 400 groups in our country. In the 1959 survey there are over 1,100. While only 3,000 doctors were involved in group practice fifteen years ago, more than 10,000 are involved now (Pomrinse & Goldstein 1960). An even clearer indication of that trend can be seen from the experience of graduating classes. The class of 1935 showed that partnership and group physicians were one-seventh the number of solo physicians, while in the class of 1950 group practice and partnerships were one-half the number of solo practitioners (Weiskotten *et al.* 1960).

But group practice simply as an alliance of specialists is not wholly satisfactory. The general practitioner offered the family a focus for centring their care and for adjusting and combining specialist activities. This role is still necessary in group practice. The family doctor approach for meeting the needs of the family for guidance and support through the maze of specialized knowledge is perhaps more necessary than ever because, concomitant with the changes in medical knowledge over the past fifty years, there have been changes in the structure of our society and in the interrelationships of families with society. The family must have access to a person with modern medical knowledge and training, but it must also have access to someone who will help them through the conflicts and helplessness which disease imposes.

Furthermore, the patterns of illness have changed. We can deal with acute diseases expeditiously and reasonably successfully. Since 1900, deaths from acute infectious disease in our own country have declined from about 25,000 to well under 10,000 at the same time that the population has increased from 75 million to 180 million (U.S.P.H.S. 1956–57). Diseases which physicians face to-day are more complex. The chronic illnesses require more knowledge of human relationships, broader understanding and sympathy with the sick person's needs as well as greater knowledge of the course of the disease itself. Chronic illness requires more supervision over longer periods of time. The physician must deal with the family and society in a way which acute illness rarely demands (Cherkasky 1953).

We are faced with the necessity for planning a medical service that will integrate modern medicine, specialism and the rapid accumulation of medical knowledge into family practice. The general practitioner in solo practice would be hard pressed to find a place in the scheme under the best of circumstances because of his lack of hospital connexions. The hospital has become the exciting centre of definitive medical care and medical education. As Evang (1960) says: 'The professional dissatisfaction of many general practitioners is also striking. . . . These complaints seem to be more pronounced among general practitioners in densely populated urban and suburban areas, and more in countries where the general practitioners do not have an opportunity of treating their own patients in hospitals.' And he adds, 'The general practitioner works in professional isolation and thereby misses the constant and positive stimulation and education embodied in teamwork with other doctors or other groups of medical personnel.'

Lord Moran, in a debate in the House of Lords in 1943, said (Turner 1959): 'If doctors . . . were to be banded eight or nine together and were to see patients at some house built for the purpose, with facilities for diagnosis and with consultative services at their elbow, they would breathe again that atmosphere of their student days in the wards and it would be a great gain to the community.'

Family practice requires social attitudes and willingness to deal with family problems, elements that need to be precisely defined and built into medical education. But family practice also requires a well-trained and adequately prepared physician who is working in a setting that allows him to use and refine his laboratory skills as a modern doctor.

With these considerations in mind it may be useful to look at the Montefiore Medical Group with particular reference to the activities of the family doctors associated with that Group. In the customary pattern of American group practice the Montefiore Medical Group is composed of specialists, the family physicians being specialists too in that they are all internists, that is, they have had four or five years of hospital experience after graduation from medical school so as to qualify them for the American Board of Internal Medicine. The Group physicians are all salaried, in accordance with a formula which takes into consideration their experience and training and the amount of work that they perform. Within these limits all physicians are paid equally. All the physicians practise in the Group Centre.

The Group's patients derive mainly from a pre-

payment scheme called the Health Insurance Plan of Greater New York and this Health Insurance Plan reimburses the Group for each subscriber covered. This capitation income is the Group's budget, and salaries as well as operating costs are part of the budget.

The family internist in the Group takes responsibility for complete care of the patient in the home, office and hospital. He has a panel of between 1,200 and 1,500 patients. His patients see him in the office or are visited in the home. If they require hospitalization they are looked after by him, in the Montefiore Hospital. This arrangement of practising from a single centre associated with the Montefiore Hospital has the advantages of formal as well as informal professional contacts among the physicians, gives all practitioners a sense of identification with the Group and an opportunity for participating in hospital activities, and continuing education.

The family physician has a fixed number of office hours, twenty-five per week. Of these twenty-five hours some are morning time, some afternoon time and some evening time. Two evenings a week, he will have hours after 6 o'clock in order to allow working people to come in without losing time and pay. One day he may have one short session and if there are no house calls, he will be free to study, attend conferences, visit another hospital or take his wife shopping.

The number of hours was arrived at pragmatically, since the average patient requires 3 family doctor services per year, 80% of which are provided in the office. A revisit is reckoned to take fifteen minutes, a physical examination thirty minutes and a new patient is entitled to two thirty-minute appointments. On the average the physician sees 3 patients an hour. While all his appointments may be booked, not all of the patients will show up. On the other hand, there will certainly be some patients who come in without appointments. In addition, he may be required to see as an emergency, a patient of one of his colleagues who is not in the office at the time. The Montefiore Group family physician thus provides about 4,500 services a year, of which perhaps 3,600 will be done in the office. Including the time necessary to make home calls and rounds in the Hospital, it is estimated that the family physician in the Montefiore Medical Group works about fifty hours a week forty-seven weeks a year. He is entitled to four weeks of vacation and up to a week to attend a medical meeting. In addition, he is entitled to four weeks of sick leave with full pay, or up to eight weeks at the discretion of the Group Executive Committee. He receives other perquisites, such as an insurance policy and a pension plan. He has a secretary to take all telephone calls and make the appointments for him.

In carrying out his daily duties, the family doctor takes care of his own patients, but he is also acting as part of a group. If one of his colleagues is sick or tied up with a special surgical procedure that makes him unavailable for a few hours, he may cover house calls for him and his colleagues will reciprocate another time. A rotating schedule provides for calls after 5 in the evenings and for weekends. Each of the family physicians is on duty one night a week and one weekend in five with two other family physicians to take care of emergency services. Some of the requests for service can be postponed and the patient will be advised to telephone his own physician the next day. Problems that cannot wait will be seen by the doctors on call and dealt with.

How busy he is will vary with the day of the week and the month of the year. Record keeping is minimal. He has to make notes in the chart, of course, fill out insurance forms or dictate letters relating to his patients. But most of the paper work is completed by clerks and the record librarians.

You may compare the picture of a group family doctor with the activities of a solo practitioner in your own experience and weigh the differences. This family doctor-internist is asked to prepare himself somewhat more extensively in medicine than the average general practitioner but the system is designed to offer him a direct channel for continuity of care of his patients in the home, office and hospital.

The salaried group structure does not impose a rigid pattern and each doctor does not do exactly the same thing under exactly the same conditions. There is in fact great variation. These 9 family doctors are very similar in their training. All have had five years of hospital training after medical school. Their ages range from 33 to 41. Five have already passed their Board in Internal Medicine. Panel size varies from 1,020 patients to 1,573. This is partly from choice, and partly because of assignment of other duties. One doctor, for example, has some administrative responsibility. But per panel member, they each provide quite different average amounts of service. One doctor provides as little as 2·6 services per subscriber per year and another doctor almost 4. Furthermore the variation in utilization is not due to differences in age, sex or occupation of the patients. Other patients' attributes may, of course, be exerting some influence. The same wide variation can be seen in the volume of X-rays or the number of blood chemistries ordered – in either case one doctor may order twice as many as another.

Since part of the doctor's job is to satisfy his patients, it would be interesting to know whether the way in which a doctor practises influences his patients' opinion of him or reaction to him. The only key we have to this in the Group is the rate of transfers of patients from one doctor's panel to another doctor's in the Group, and here again there is wide variation, though the rates of change of doctor are so small that the overall impression is one of great satisfaction.

I hesitate to draw any far-reaching conclusions from this material. More extensive information is needed to rule out such artifacts as sampling errors and to seek the reasons for the variations that persist over time. However, for my present purposes the data in hand are adequate. They give support to my main thesis that in a group practice setting such as ours the physicians do not conform to a rigid pattern of medical care and the art in medicine is not lost.

In England a great deal of emphasis is being placed on training for general practice, for example, the excellent programme of Scott (1956) in Edinburgh. In America, too, the American Academy of General Practice (1957) is urging the American Medical Association to adopt a policy of general practitioner training which is not far removed from British ideas. However, I would like to emphasize that family practice must be through group practice in a hospital setting. The recently published Sluglett report (1960) shows concern for creating groups of doctors based on health centres, which is a way along this line. It would be valuable to develop a group practice demonstration in a hospital setting in England. Much experiment needs to be done. Recently, in the *Lancet* I proposed a new type of curriculum for family practice (Silver 1961). Orientating students toward family medicine and developing a specialty of family practice will be helpful in creating the kind of practitioners we need. But a variety of patterns of practice also should be tried. For example, over an eight-year period we had a demonstration at Montefiore Hospital in which a public health nurse and a social worker augmented the internist's job in a health team practice (Silver 1958). The full appropriate use of public health nurses in family practice is still to be tried.

REFERENCES

American Academy of General Practice (1957) *G.P.* **15**, April, p. 141
Backett E M (1960) *Lancet* ii, 1075
Cherkasky M (1953) *Med. Clin. N. Amer.* **37**, 631
Collings J S (1950) *Lancet* i, 555
Evang K (1960) Health Service, Society and Medicine. London
Fox T F (1960) *Lancet* i, 743
Logan R (1960) *Manchr med. Gaz.* **40**, October (unpaged)
Means J H (1953) Doctors, People, and Government. Boston
Pomrinse S D & Goldstein M S (1960) A Report of the 1959 Survey of Group Practice (presented at annual meeting of A.P.H.A., Nov. 2, 1960; mimeographed)
Scott R (1956) *J. med. Educ.* **31**, 621
Silver G A
(1958) *Yale J. Biol. Med.* **31**, 29
(1961) *Lancet* i, 271
Sluglett J (1960) Health Centre Report (Medical Practitioners Union; mimeographed)
Taylor S (1954) Good General Practice. London
Turner E S (1959) Call the Doctor. New York
U.S.P.H.S. (1956-7) *Vital Statist. spec. Rep.* **46**
Weiskotten H G, Wiggins W S, Altenderfer M E, Gooch M & Tipner A (1960) *J. med. Educ.* **35**, 1071

Meeting February 15 1961

A discussion was held on **The Early Diagnosis of Congenital Abnormalities**; the opening speakers were Dr Margaret Dudley-Brown (*York*), Dr H G Farquhar (*Liverpool*) and Dr Ronald Mac Keith (*London*). A short account of the meeting appears in the *Practitioner*, 1961, **186**, 499.

Section of Epidemiology and Preventive Medicine

President J A Fraser Roberts MD

Meeting December 16 1960

Discussion on Congenital Pyloric Stenosis [*Summary*]

Professor Thomas McKeown (*Birmingham*)

Infantile Hypertrophic Pyloric Stenosis

For many years the literature has contained reports of certain striking observations on the ætiology of infantile pyloric stenosis: the higher incidence in males than in females; the apparently increased susceptibility of first-born children; and the anomalous relationship between the presence of a tumour and the occurrence of symptoms.

These observations were confirmed and extended on data consisting of all cases of pyloric stenosis identified in Birmingham hospitals in the ten-year period 1940–49. The incidence was approximately 3 per thousand live births and the proportion of males 80%. From about two weeks after birth the condition was considerably more common in first-born than in later born children (McKeown *et al.* 1951*a*).

The association between incidence and birth order was interpreted as evidence of an environmental influence, but left open the question whether this influence occurred before or after birth. Observations made at operation suggested that the tumour developed after birth, since the size of tumours increased with increasing age at the time of operation (McKeown *et al.* 1951*b*, Gerrard *et al.* 1955). It was also shown that symptoms occurred earlier in children born at home than in those born in hospital (McKeown *et al.* 1952).

The incidence of pyloric stenosis was raised in sibs of affected (about twenty times) but not in cousins (McKeown *et al.* 1951*c*). It was substantially higher in children of affected parents than in children of those not affected (Carter & Powell 1954), the risk being considerably greater if the affected parent was the mother (McKeown & MacMahon 1955). Twin data suggested that the frequency of concordance when one twin had pyloric stenosis was little higher in monozygotic than in dizygotic pairs (MacMahon & McKeown 1955).

Although the high proportion of males among children with pyloric stenosis leaves no doubt about the significance of genetic constitution, the familial data are inconsistent with any simple genetic hypothesis. The association with birth order, place of birth and sex of affected parent is strongly suggestive of environmental influences, presumably manifested during the first few weeks after birth.

REFERENCES
Carter C O & Powell B W (1954) *Lancet* i, 746
Gerrard J W, Waterhouse J A H & Maurice D G (1955) *Arch. Dis. Childh.* 30, 493
McKeown T & MacMahon B (1955) *Arch. Dis. Childh.* 30, 497
McKeown T, MacMahon B & Record R G (1951*a*) *Ann. Eugen., Lond.* 16, 249
(1951*b*) *Lancet* ii, 556
(1951*c*) *Ann. Eugen., Lond.* 16, 260
(1952) *Arch. Dis. Childh.* 27, 386
MacMahon B & McKeown T (1955) *Acta Genet. med. Gemell.* 4, 320

Dr Cedric O Carter (*London*)

Genetic Factors in Pyloric Stenosis

The data available hitherto for any discussion on the genetics of pyloric stenosis may be summarized as follows: The concordance rate for monozygous twins, though higher than that for dizygotic twins, is probably less than 50%. The incidence of pyloric stenosis in England is about 5 per thousand male and about 1 per thousand female infants. The incidence for brothers and sisters of patients is from ten to twenty times higher than the incidence in the general population.

In recent years it has become possible to collect additional data, essential to any genetic hypothe-

sis, on the incidence in the sons and daughters of patients. We are in touch with over 500 such males and nearly 100 such females who were successfully treated by Rammstedt's operation at The Hospital for Sick Children between 1920 and 1939, and have visited the families of the 174 men and 48 women who have already had children. The information on the brothers and sisters and the sons and daughters of these index patients is summarized in Tables 1 and 2.

Table 1
Relatives of 174 male index patients

	Brothers	*Sons*	*Sisters*	*Daughters*
Affected	5	11	5	2
Total	156	162	165	161
% affected	3·2	6·8	3·0	1·2

Table 2
Relatives of 48 female index patients

	Brothers	*Sons*	*Sisters*	*Daughters*
Affected	5	9	1	4
Total	38	44	40	36
% affected	13·2	20·5	2·5	11·1

The diagnostic criteria for calling a relative 'affected' were strict; in most cases the presence of a pyloric tumour was confirmed at Rammstedt's operation, but a few cases, medically treated, were included where a pyloric tumour was felt by an expert.

With male index patients, the incidence of pyloric stenosis in brothers and sons is about ten times, and in sisters and daughters about twenty times, the incidence in the general population. With female index patients, the corresponding ratios are about thirty times and about sixty times the incidence in the general population.

These findings indicate neither recessive nor sex-linked inheritance, but several genetic models could be used to explain them. One of the simplest is to assume that a single main 'dominant' gene and a multifactorial background together provide the genotype underlying predisposition to pyloric stenosis. The multifactorial background is presumably for a character which is modified by sex, and the author and his colleagues have been impressed by the athletic ability of many of these patients, both men and, relative to their sex, women. At the moment this is only a clinical impression, and it is planned to investigate the matter further.

Meeting January 20 1961

Paper

The Epidemiology of Rheumatoid Arthritis in Northern Europe

by J S Lawrence MD MRCP, V A I Laine MD and R de Graaff MD[1]

Despite extensive investigation by clinicians, pathologists, biochemists and immunologists the causative factors in rheumatoid arthritis remain obscure. Recently epidemiological techniques have been brought to bear on the problem and are producing valuable pointers both on the environmental and the genetic factors involved.

Methods: In earlier studies, notably the survey by Newman in 1924, data were collected by general practitioners on insured patients seeking advice for rheumatic symptoms. This method has the advantage of economy but has the serious disadvantage that many patients are missed since they do not attend their doctor, often despite quite extensive disease. The disadvantage is overcome if the survey is based on home interviews made by social workers of a sample of the population, as in the survey undertaken by the Central Office of Information (Stocks 1949). This in turn has the disadvantage that diagnoses are based on statements by the respondent and the accuracy of the diagnosis is therefore open to doubt.

The method may be extended by including a subsequent visit by a physician to all those with rheumatic complaints, as in the original survey of rheumatic complaints in the town of Leigh in Lancashire, which was based on a 1 in 10 sample of households (Kellgren *et al.* 1953). This gives a useful indication of the size of the problem and of the relative importance of different rheumatic diseases as causes of incapacity. The method has been developed particularly in the Netherlands where a 2% sample of the entire population of the country has been investigated (de Graaff 1960).

Though useful from the economic standpoint, the method has rather limited value as a method of investigating causative factors. The reasons for this are twofold: (1) The data depend partly on

[1]From: The Empire Rheumatism Council Field Unit, Manchester University; The Rheumatism Foundation Hospital, Heinola, Finland; and the 'Gezondheidsorganisatie T.N.O.' The Hague. The Netherlands.

the complaint thresholds of the individuals, which may vary considerably in different areas and in different occupational groups in the same area. In Leigh, for example, it was found that rheumatic complaints were only half as frequent in miners' families as in the rest of the population, despite identical X-ray changes. (2) The diagnostic standards of physicians vary greatly one from another and in the same physician from time to time, so that no reliable comparison between different groups is possible.

Criteria: For these reasons it has been necessary to introduce more precise criteria into surveys of rheumatoid arthritis in population samples. In 1956 a committee of the American Rheumatism Association (A.R.A.) introduced criteria for rheumatoid arthritis based on a study of the symptoms and signs in 332 patients (Ropes *et al.* 1958). Points were given for morning stiffness, pain on movement of a joint, joint swelling or effusion, subcutaneous nodules, X-ray changes typical of rheumatoid arthritis, a positive sheep-cell agglutination test and certain changes in the synovial fluid and on biopsy of nodules or of the synovial membrane. It was decided that a score of 5 or more points should indicate definite disease, 3–4 points probable and 2 points possible disease. These criteria have now been used in a number of population surveys and have proved of great value but are not entirely free from inaccuracies due to observer difference. For this reason, reliance has tended to be placed more on the radiological and serological findings.

Radiology: The radiological diagnosis of rheumatoid arthritis depends mainly on the recognition of erosions of bone. These are found chiefly at the joint margin and can be seen most clearly in the metacarpal and metatarsal heads. They must be differentiated from bone cysts which are common and are usually associated with osteoarthrosis or trauma. Cartilage erosion is also of value, but can be recognized only when it is sufficiently diffuse to cause narrowing of the joint space and must be differentiated from cartilage wear due to osteoarthrosis. Osteoporosis is also a feature of rheumatoid arthritis but, except where it is confined to the immediate neighbourhood of the joints, is more often due in population samples to other causes. Other less common signs are the formation of periosteal new bone in the region of affected joints, and soft tissue swelling, but these are more usually found in the active stage and are thus less frequent in population samples. In the spine there is ankylosis of the apophyseal joints with subluxation at the disc above or below the immobile joint and sometimes diminished disc space. In surveys of rheumatoid arthritis these three sites should be X-rayed as a routine. The other joints are less important.

For survey purposes all X-ray changes have been graded 0–4 and each group of joints, e.g. the proximal interphalangeal joints of the fingers, is read not only for rheumatoid arthritis but also for osteoarthrosis, porosis, erosions and gout, the grading being based on the worst affected joint.

Unfortunately in reading X-rays also considerable observer differences arise. In a comparison of the readings of a series of radiographs for osteoporosis, erosions and rheumatoid arthritis by six experienced observers, wide disagreement both in grading and interpretation was noted (Kellgren 1956). Reassessment of the same films by one observer, after an interval of one year, showed a closer agreement and it was evident that if a comparison of two series of X-rays is to be of any value they must all be read by one observer. It was clear, however, that appreciable changes in grading by one individual could occur over a period of time and that if differences between populations are to be established their films must be read at the same time, preferably mixed so that the observer is unaware of their origin.

To establish international radiological criteria for rheumatoid arthritis, a series of hand X-rays were presented at the International Congress of Rheumatic Diseases in Toronto in 1957. Rheumatologists were asked to grade the films into 5 categories as follows:

0 = Definite absence of rheumatoid arthritis
1 = Doubtful rheumatoid arthritis
2 = Definite but minimal rheumatoid arthritis
3 = Moderate rheumatoid arthritis
4 = Severe rheumatoid arthritis

On the answers to this questionnaire four films, giving modal values for each grade, were chosen for use as standards (Kellgren & Lawrence 1957). Standards have also been produced for spinal rheumatoid arthritis (Sharp *et al.* 1958), since the radiographic appearances differ from those in the peripheral joints. These standards are being made available in the form of an atlas together with those for other rheumatic diseases.

Serology: Two types of serological test have been used in rheumatoid arthritis: (1) The sheep-cell agglutination test (SCAT), which depends on the ability of certain rheumatoid sera to agglutinate sheep or human red cells sensitized by anti-sheep or human erythrocyte rabbit serum. (2) The latex (LFT) or bentonite flocculation test (BFT), which depends on flocculation by certain rheumatoid sera of latex or bentonite particles coated with modified human γ-globulin. The SCAT is positive in some 70% of patients attending hospital in

whom a diagnosis of rheumatoid arthritis has been confirmed, the LFT and BFT in 80%.

Surveys of Rheumatoid Arthritis in Northern Europe
The radiological surveys so far undertaken are shown in Table 1. The total sample is 4,536 of whom 3,999 have been examined, a completion rate of 88%. Those who had only a clinical examination have been excluded from the completion rate and from the subsequent assessment of results.

Dr R de Graaff: the Pneumoconiosis Research Unit has examined rural samples in Annandale in Scotland and in the Vale of Glamorgan in South Wales. There have also been a number of genetic studies which will be described later.

Age and sex distribution: The Leigh and Wensleydale samples have been used to study the age and sex distribution of rheumatoid arthritis (Table 2). In both sexes the prevalence of probable and definite disease, as determined by the A.R.A.

Table 1
X-ray surveys of population samples

Locations	*Age distribution*	*Method of sampling*	*Number available*	*Number examined*	*Completion rate*
Leigh	15+	Random 1 in 30	1,565	1,343	86%
Wensleydale	15+	Area	1,025	891	87%
Rhondda	Males 35–64	Stratified	586	522	89%
	Females 55–64	Random 1 in 7	295	261	88%
Heinola	55–64	Random 1 in 2	361	346	96%
Rotterdam	55–64	Random 1 in 47	305	275	90%
Annandale	55–64	Random 1 in 4	199	186	93%
Glamorgan	55–64	Random 1 in 3	200	175	88%
Total	15+		4,536	3,999	88%

The largest survey was undertaken in the town of Leigh in Lancashire in the years 1954–9 and was based on a 1 in 30 sample of the adult population. There was a total of 1,565 persons of whom 1,343 were examined giving a completion rate of 86%. Between the years 1958–60, an area sample was examined in a rural population in Wensleydale. This included the southern half of the town of Hawes and half the villages and farms in the area. In 1958 a survey was undertaken in the Rhondda in conjunction with the Pneumoconiosis Research Unit. In this survey the males were aged 35–64 and were stratified for occupation so that half were miners and half non-miners; the females were aged 55–64. The remaining surveys are all based on random samples of the 55–64 age group; a rural sample of 361 in the village of Heinola in Finland was undertaken by Dr V Laine, and an urban sample of 305 in Rotterdam in Holland by

Table 2
Prevalence of rheumatoid arthritis as defined by the A.R.A. criteria in combined urban-rural population

	Males			*Females*		
		Probable or definite rheumatoid arthritis			*Probable or definite rheumatoid arthritis*	
Age	*Total examined*	*Cases*	*%*	*Total examined*	*Cases*	*%*
15–24	174	1	0·6	178		0
–34	178	2	1	176		0
–44	185	2	1	214	4	2
–54	235	8	3	227	9	4
–64	143	7	5	179	26	15
65+	145	6	4	200	32	16
Total	1,060	26	2·5	1,174	71	6·0

criteria, increased with age, starting at the age of 20 in the males and reaching a maximum of 5% in the 55–64 age group. In the females there was none below the age of 35 but thereafter the increase was more rapid so that, of those over 65, 16% had probable or definite disease. Taking all ages, the disease was two and a half times as common in females.

Radiological evidence of erosive arthritis in the hands and feet showed a similar relationship to age (Table 3). There was an earlier onset in males of whom 12 had grade 2–4 change in the first three decades, compared with only 2 females. After the age of 65 the condition had a higher prevalence in females so that the prevalence in the population sample as a whole was identical in the two sexes, amounting to 3%. There was, however, rather more grade 4 disease in the females.

Table 3
Radiological evidence of erosive arthritis – hands and feet – Leigh and Wensleydale

	Males						*Females*					
		Grade						*Grade*				
Age	*Total X-rayed*	*2*	*3*	*4*	*2–4*	*%*	*Total X-rayed*	*2*	*3*	*4*	*2–4*	*%*
		Cases						*Cases*				
15–24	165				0		172				0	
–34	177		1		0·6		174				0	
–44	184	2			1		214			1	0·5	
–54	234	8		1	4		226	1			0·4	
–64	141	5	1	1	5		178	4	2	2	4	
–74	94	6	2		9		137	14	1		11	
75+	47	3	1		9		57	5	1	3	16	
Total	1,042	24	5	2	3		1,158	24	4	6	3	

In the cervical spine radiological evidence of rheumatoid arthritis was found in 5% of males and 5% of females (Table 4). This was the most frequent site of the disease as judged by X-ray. As in the peripheral joints it was related to age, occurring in 1% of those in the 15–24 group and reaching a maximum of 22% in the oldest age groups. Unlike the changes in the hands and feet the onset was not earlier in males, there being no significant difference between the sexes at any age group. The cervical changes were, however, more often minimal in the males. Other sites were much less often affected.

Table 4
Age and sex distribution of radiological evidence of erosive arthritis in the cervical spine in Leigh and Wensleydale

	Males				*Females*			
		Grade				*Grade*		
	Total	2	3–4	2–4	*Total*	2	3–4	2–4
Age	*X-rayed*	*Cases*		%	*X-rayed*	*Cases*		%
15–24	165			0	170	2		1
–34	176			0	172			0
–44	183	1		0·5	213		1	0·5
–54	233	6		3	224	7	1	4
–64	139	10	1	8	174	8	3	6
–74	93	15	3	19	137	21	6	20
75+	47	9	4	28	57	12		21
Total	1,036	41	8	5	1,147	50	11	5

Serum tests: The SCAT was positive in 3·7% of males and 4·4% of females, the BFT in 4% of either sex. Both the SCAT and the BFT show an increasing titre with age but neither shows a sex difference at any age group, the proportion of positive tests being identical in males and females. The age distribution of positives in the mixed urban-rural population shows a stepwise increase between the ages of 15 and 74, with peaks every twenty years to a maximum of 11% of positives in males and 9% in females in the older age groups (Lawrence 1960). The BFT has so far been tested on only 383 sera from population samples but shows a similar increase with age and a similar twenty-year periodicity. The reason for this periodicity in serum tests for rheumatoid factor is by no means clear nor is the increase with age understood. It does not appear to be due to enhanced survival of seropositive individuals since there were only 3 positive SCATs in the 15–24 age group in the population, whereas there were 20 in the 65–74 year age group. Nor have individuals as opposed to populations an increasing titre with age in the population samples. In a five-year follow-up of 57 persons from the population of Leigh, the SCA titre was found to have risen in only 5, but it had become less in 16. This of course requires follow-up over a longer period, but if it is confirmed some other theory will have to be evolved. One possibility is that the sheep-cell titre depends on past exposure to some antigen which has become less frequent over the last seventy years so that the older members of the population stand a greater chance of having acquired a positive test. This theory might also explain the twenty-year periodicity. Certain infections – tuberculosis, syphilis and gonorrhœa, for example – have shown an increase during each world war and would thus have had approximately a twenty-year periodicity. An association between the SCAT and infection has been demonstrated in experimental animals. Hæmagglutinating factor can be induced in, for example, a proportion of rabbits by immunization with streptococci of group A and by various anaerobic bacteria and in rats by infection with a strain of *Streptobacillus moniliformis*. This occurs, however, only if *S. moniliformis* has been grown in the presence of human proteins. The factor reacts both with human F II globulin and with rabbit anti-erythrocyte globulin (Eyquem *et al.* 1959, Lerner *et al.* 1960).

The relationship of the SCAT to the BFT is also complex. In a series of 383 persons from the Wensleydale sample studied by Burch, Ball & Block (personal communication) in which both tests were used, the BFT was positive and the SCAT negative in 10, the SCAT only was positive in 4 and both tests were positive in 6. There were more in whom both tests were positive in the population sample than would be expected by chance so that it is evident that some factor is shared in common. This factor is not rheumatoid arthritis since only 1 of the 6 in whom both tests were positive had clinical or radiological evidence of the disease. A similar degree of association has been found between the SCAT and LFT (Valkenburg & Ball 1961). The association may be chemical since both tests depend on the presence in the serum of a fast migrating macroglobulin, having a sedimentation constant of 19S which exists *in vivo* as a soluble combination with 7S γ-globulin (Franklin 1960).

The association between rheumatoid arthritis and the serum tests is similarly obscure. Only one person in 3 with a positive SCAT in the random samples of Leigh and Wensleydale had clinical or radiological evidence of rheumatoid arthritis, so it is unlikely that the serum factor is produced by the disease. There is evidence, however, that a positive SCAT predisposes to rheumatoid arthritis. Of 19 seropositives in Leigh who were followed up for five years, 8 had rheumatoid arthritis in 1954 but by 1959 2 more had developed evidence of the disease. Of 19 with negative SCATs, 3 had rheumatoid arthritis in 1954 but only 2 in 1959, and of 19 with doubtful titres, 2 had rheumatoid

arthritis in 1954, 1 in 1959. Thus, of those with a negative test, none had developed the disease but in 2 it had cleared up completely. The predisposition, if such there be, would seem to be quantitative. In the Leigh and Wensleydale samples all those with a titre of 1 in 512 had definite disease.

Geographical distribution: Information on geographical distribution is available mainly on the 55–64 year age group in Northern European countries (Table 5). Definite rheumatoid arthritis (by the A.R.A. criteria) showed much the same prevalence, between 2% and 3% in all surveys undertaken, but when 'probable' disease was included the disease was twice as common in Leigh as in any other area ($\chi^2=8{\cdot}2$, $P<0{\cdot}01$). It is difficult to be certain how much of this is due to observer difference in assessing physical signs. The difference was most striking in the females. Of the 30 females with probable disease in Leigh, 11 were given a confident diagnosis of rheumatoid arthritis at the time and 9 were considered doubtful. This may be compared with the Rhondda where there were only 13 females with probable disease. Only 3 of these were given a confident diagnosis of rheumatoid arthritis and 6 were considered doubtful. Observer differences may, however, have played a part in the clinical diagnosis of rheumatoid arthritis.

When observer difference is excluded by using only the X-rays, which were all read by the same observer, the prevalence in Leigh is seen not to be unduly high. Indeed rheumatoid arthritis of the cervical spine was less frequent in Leigh than in any of the other surveys. There was significantly less change in the hands in Rotterdam and the Vale of Glamorgan, the two most southerly areas to be surveyed, and it is of interest that the sheep farmers of Wensleydale and their families most often had X-ray changes in the hands. This may well be a climatic effect determining the site of the disease rather than its total prevalence. X-ray changes in the feet were not strikingly different in the areas studied.

The SCAT results are of some interest. Although the geographical differences in titre were not striking, they were significant ($P\simeq 0{\cdot}02$), the urban populations having 5% of positive tests, the rural areas 2–3%. Here observer difference can be excluded with some certainty since all tests were made by Dr J Ball of the Rheumatism Research Centre in Manchester.

Family studies: The occurrence of rheumatoid arthritis in families has been known for some time. Kroner (quoted Falls 1953) reported rheumatoid arthritis in four generations of one family and Papp & Tepperberg (1937) in another family recorded 11 persons in four generations. Numerous comparisons have been made between rheumatoid arthritic and control families (Lewis-Faning 1950, Short *et al.* 1952, Stecher *et al.* 1952, Barter 1952, Miall 1955, de Blécourt 1961). All have found a higher prevalence in the rheumatoid relatives.

In a survey carried out by the Empire Rheumatism Council Field Unit of families of persons with rheumatoid arthritis or a positive SCAT discovered in the population samples in Leigh (Lawrence & Ball 1958), 183 out of a total of 209 adult relatives (parents, siblings and offspring) living in the area were examined. The completion rate was thus 87% and was therefore similar to that in the random samples. They were compared with controls taken from the random samples and matched by age and sex with the relatives. These controls were stratified for clinical arthritis and sheep-cell test in each age group against the random sample.

The relatives of seropositive arthritics had four times as much clinical disease as the controls, the families of seronegative arthritics had only twice

Table 5

Prevalence of rheumatoid arthritis in 55–64 age group in Northern Europe

	Urban						*Rural*							
	Leigh		*Rhondda*		*Rotterdam*		*Heinola*		*Wensleydale*		*Glamorgan*		*Annandale*	
Total	394		360		275		346		117		175 (87)●		186	
A.R.A. criteria		%		%		%		%		%		%		%
Definite	13	(3)	9	(3)	9	(3)	7	(2)	3	(3)	2	(2)		—
Probable and definite	55	(14)	26	(7)	23	(8)	24	(7)	7	(6)	6	(7)		—
Radiological changes														
Cervical spine	30	(8)	28	(8)	24	(9)	33	(10)	11	(9)	13	(15)		—
Hands	8	(2)	11	(3)	1	(0·4)	11	(3)	6	(5)	1	(0·6)	2	(1)
Feet	13	(3)	18	(5)		—	11	(3)	3	(3)	3	(2)	3	(2)
Positive SCAT	19	(5)	18	(5)	12	(4)	7	(2)	3	(3)	6	(3)	3	(2)

● In Glamorgan only the 87 females were examined clinically and had a radiograph of the cervical spine.

Table 6
Rheumatoid arthritis in relatives of persons with arthritis or a positive SCAT

Propositi	*Total relatives*	*Clinical arthritis*	%	*Erosive arthritis (hands or feet)*	%	*Positive SCAT*	%	*Osteoarthrosis 5+ joints*	%
Seropositive arthritis	43	7	(16)	6	(14)	7	(16)	5	(12)
Seronegative arthritis	88	7	(8)	1	(1)	5	(6)	9	(10)
Positive SCAT without arthritis	52	2	(4)	5	(10)	12	(23)	3	(6)
Total relatives	183	16	(9)	12	(6)	24	(13)	17	(9)
Expected number●	183	7	(4)	6	(3)	9	(5)	13	(7)

●The expected number is derived from the random sample of the population of Leigh adjusted for age and sex to correspond with the total relatives.

as much and the seropositive non-arthritic families the same amount as the controls (Table 6). Only the seropositive arthritic families had *significantly* more than the controls and there was no significant difference between the families of seropositive and seronegative arthritics in this respect.

Radiological evidence of rheumatoid arthritis was more than four times as common in the seropositive arthritic families as in the controls. In the seronegative families it was found in only one case but in the seropositive non-arthritic families it was three times as common as in the controls. Here again only the seropositive arthritic families had significantly more than the controls.

The SCAT was positive four times as often in the seropositive families as in the controls and was just as often positive in the non-arthritic as in the arthritic families. In the seronegative families on the other hand, there was no excess of positives.

Bremner *et al.* (1959), who compared relatives of hospital patients with seropositive and seronegative rheumatoid arthritis, found rather more clinical arthritis in the seronegative group, but like us they found more radiological disease and positive serology in the other group. Though the differences in this survey were not significant, they indicate, when taken in conjunction with our own findings, that in both seronegative and seropositive families there is more clinical disease than in the population as a whole but that only in the seropositive relatives are there more erosive changes or positive serology.

Multiple osteoarthrosis was found in both seropositive and seronegative arthritic families about twice as often as in the controls but was not increased in the seropositive non-arthritic families. It thus resembled rheumatoid arthritis in its distribution. It is of interest in this connexion that siblings of persons with generalized osteoarthrosis frequently have inflammatory polyarthritis and that this is nearly always seronegative (Lawrence 1961).

What is the cause of this familial aggregation of rheumatoid arthritis and of the SCAT? If it were environmentally determined it would be expected that both husband and wife would be affected in a proportion of families. In fact in only two families were both husband and wife found to have a positive SCAT in Leigh and Wensleydale where some 1,200 married persons were examined in the random sample. The prevalence of positive tests was 4% or 1 in 25 in married persons in these samples, so that by chance both spouses would be expected to be positive once in 625 matings, a close approximation to what was found. In no instance did the sheep-cell-negative form of polyarthritis occur in both spouses in the population of Leigh and Wensleydale, though, since 1 person in 34 has this type of arthritis, it should have occurred once in this size of population sample. Thus it is unlikely that environment, at least during adult life, is responsible for this familial aggregation. Environmental factors in childhood offer a possible explanation and this is at present under investigation in a number of centres in the United Kingdom and the Netherlands, under a scheme devised by Dr A Dixon and supported by the Empire Rheumatism Council. To this end the prevalence of clinical and radiological arthritis and of positive serological tests will be assessed in a series of monozygotic and dizygotic twins. There have been several twin studies in the past, notably by Berglund (1940), Edström (1941), Grossman *et al.* (1956) and Thymann (1957). Most report concordance and Kaufmann & Scheerer (1928) reported that this was greater in monozygotic twins but there is little objective information. Edström reported concordance in 3 of 5 monozygous pairs but in only 1 of 9 dizygous pairs of twins.

If the familial aggregation is genetically determined it would seem likely that more than one locus is involved. There would appear, for example, to be one factor favouring the appearance of clinical arthritis with or without secondary osteoarthrosis. It is tempting to assume that this is sex-linked and is a dominant on the X-chromosome since both clinical arthritis and generalized non-nodal osteoarthrosis are more common in females. If this were so, it would be passed by affected mothers equally to their sons and daughters, but by affected fathers only to their daughters. Rare instances have been recorded in which father and son have had clinical disease and this would appear to negative this type of inheritance but it is of course possible that the disease is not homogeneous and that an acquired form also exists.

Table 7
Sheep-cell agglutination titres in first-degree relatives of persons in the population sample of Leigh

Propositi	*Relatives*		
Titre	*Total in sample*	*Total tested*	*Titre 32+*
<4	363	207	3%
4	99	87	
8	42	39	6%
16	31	23	
32	158	124	10%
64	60	32	
128	59	40	
256	33	26	12%
512	11	8	

If the sheep-cell factor is inherited, it is in all probability a multifactorial inheritance. The evidence for this is: (1) That the distribution of sheep-cell titres in the population presents as a continuous variable (Kellgren & Lawrence 1956). Some 60% of the population have no reactant by this test and there is a progressive diminution in the number of persons reacting as the titre is increased. (2) There is a direct and continuous relationship between the titre in the propositus and the relatives (Table 7), varying from 3% of positive tests in relatives of those without reactant in their serum to 12% in those with a titre of 128 or more.

Benign Polyarthritis

In random population samples, in addition to those who have obvious polyarthritis, there is a group who give a history of polyarthritis but in whom the symptoms have completely subsided. This group, though less amenable to direct epidemiological study, is of considerable importance to the community. In the population of Leigh it was responsible for more frequent incapacity than rheumatoid arthritis (Fig 1). Such a history of past polyarthritis was given by 84 persons (5% of males and 7% of females) in the Leigh population sample (Lawrence & Bennett 1960). Although many of these stated that their illness was rheumatic fever, only 4 had mitral stenosis. On the other hand, 15 had joint residua on clinical examination. The prevalence of these joint residua was five times as great in persons with a history of polyarthritis as in the rest of the population and moreover they were found at an earlier age. They included subluxation of the interphalangeal and metatarsophalangeal joints and pain or limitation of movement of the metacarpophalangeal joints, wrists, knees, tarsal joints and cervical spine. Only 3 of these 84 persons had frank rheumatoid arthritis. Erosive joint changes in the hands or feet were not common in persons with a past history of polyarthritis and none showed the residual

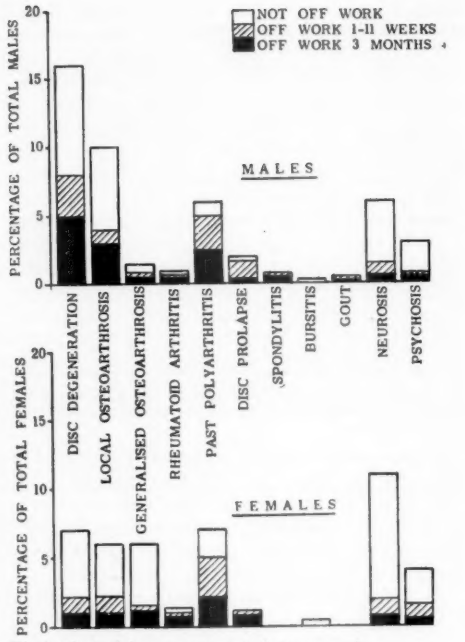


Fig 1 *Clinical diagnoses in population sample (grades 3–4)*

joint changes described by Jaccoud (1869) and by Bach (1935) and Bywaters (1950) as occurring after rheumatic fever. Altogether 9% of males and 10% of females had definite radiological changes in the cervical spine of the type usually associated with rheumatoid arthritis, compared with 3% and 4% respectively in the rest of the population. Thus the condition appeared to be related more to rheumatoid arthritis than to rheumatic fever. The SCAT, however, was positive in only 6% of males and 9% of females, little more than in the general population.

Ætiology: The onset of this transient type of polyarthritis in both sexes was mainly between the ages of 5 and 24. After the age of 24 the incidence fell sharply and in only 9 did the condition appear after the age of 45. This variation was partly but not wholly due to the smaller numbers at risk in the older age groups. Those with joint residua tended to have their attacks rather late in life. Those with cardiac residua, on the other hand, all had their attack between the ages of 5 and 24.

The season of onset, in those who could remember it, was mainly in the winter from January to March. The onset was rather earlier than in rheumatic fever but fitted closely the data given by Short *et al.* (1957) for exacerbations of rheumatoid arthritis. A study of the year of onset indi-

cated that the condition had existed at least since 1885. The greatest incidence was between 1905 and 1914 but there was no evidence that the condition ever attained epidemic proportions or that it was declining, though cardiac complications were less frequent since 1935. This is in conformity with known trends in rheumatic fever incidence. There was no definite evidence that joint residua were becoming less, except in the last ten-year period.

There is no evidence of any regional differences in prevalence, this being much the same in Wensleydale and South Wales as in Leigh.

Apart from inflammatory residua, there was found in persons with a past history of polyarthritis a greater prevalence of osteoarthrosis particularly in females. This tendency was not greater in those who had their attack late in life.

Clinical features: In its acute form this benign polyarthritis could not readily be distinguished from rheumatic fever. In the less acute type the joint symptoms persisted, many patients being off work for a year or more because of joint symptoms. A common sequence was pain which started in the feet and spread to the ankles and knees, sometimes to the hands. Severe pain in the back, neck and shoulders was often mentioned, suggesting that the spinal joints were affected. The attacks were usually single but up to 8 relapses have been recorded. Although minimal rheumatoid changes were common, only 3 of the 84 persons with a history of polyarthritis had moderate or severe rheumatoid disease at the time of examination. The prognosis is thus excellent.

Although this benign form of polyarthritis would appear to be more common than true rheumatic fever as judged by a comparison of cardiac and joint residua, it should be pointed out that those persons who had died from rheumatic heart disease would automatically be excluded from the population sample. From the *Report of the Ministry of Health* (1957) it would be expected that some 18 persons in a population sample of the size used in this study would die of rheumatic heart disease over the period of seventy years covered by our survey. Thus the original sample might have been 102 of whom 22 developed heart disease and 18 died. It would thus appear that at least as many of the original cases developed cardiac as arthritic residua and that rheumatic fever and benign polyarthritis have roughly the same prevalence.

The cause of this benign form of polyarthritis is uncertain. The seasonal incidence would suggest an infection. Benign forms of polyarthritis have been reported in virus infections such as rubella, measles and infective hepatitis (Geiger 1918, Hope Simpson 1940, Bennett & Copeman 1940, Loudon 1953, Lewis 1954, Lloyd 1960). It would thus seem possible that this is an abnormal immune response to some quite common infection.

The relationship of benign polyarthritis to rheumatoid arthritis is also uncertain. All those in the Leigh sample with a past history of polyarthritis and a positive SCAT had clinical evidence of persistent rheumatoid arthritis (grades 1–4) and it may well be that the possession of a positive SCAT or other predisposing factor such as psoriasis, for example, determines whether the arthritis clears after a time or persists. Until rheumatoid serum factors have been followed up for many years it will not be possible to determine whether this is the true explanation.

Summary

The prevalence of rheumatoid arthritis has been assessed clinically, radiologically and by means of the sheep-cell agglutination test (SCAT) in seven population samples in the United Kingdom, Finland and the Netherlands. Two of these surveys included all persons from age 15 onwards. In the remaining 5, complete radiological and serological data are available only on the 55–64 age group. The total number of persons in these samples was 4,536 of whom 3,999 were examined, a completion rate of 88%.

In the population samples in Leigh and Wensleydale, in which all age groups from 15 onwards were included, 2·5% of males and 6·0% of females had definite or probable rheumatoid arthritis as defined by the American Rheumatism Association criteria. Radiological evidence of erosive arthritis was encountered in the hands or feet in 3% of males and 3% of females but severe grades were more often encountered in the females. Radiological evidence of cervical rheumatoid arthritis was found in 5% of males and 5% of females. Other sites were much less frequently affected. The SCAT was positive in 3·7% of males and 4·4% of females. The proportion of positive tests rose with age, reaching a maximum of 11% positive in males and 9% in females in the older age groups. Only a third of those with a positive SCAT had clinical or radiological evidence of rheumatoid arthritis.

There was no difference in the prevalence of 'definite' rheumatoid arthritis in the 6 population samples in Northern Europe on which full clinical data are available. Radiological evidence of rheumatoid arthritis in the cervical spine also showed no significant geographical difference, but there was significantly more erosive arthritis in the hands in the Wensleydale sample than in the population samples in Rotterdam and the Vale of

Glamorgan. The SCAT was more often positive in the urban populations of Leigh, the Rhondda and Rotterdam than in the rural population samples.

Aggregation of rheumatoid arthritis and positive SCATs in families is discussed and the relationship of rheumatoid arthritis to the benign forms of polyarthritis commonly encountered in population samples is considered.

Acknowledgments: We are indebted to Dr J Ball of Manchester and Dr T A Burch and Dr K Bloch of Bethesda for permission to quote their serological findings on the population samples reviewed in this paper, also to Dr I T T Higgins of the Pneumoconiosis Research Unit and to Dr J B Cochran of Dumfries for clinical details of their Annandale survey and permission to use their X-rays and sera.

REFERENCES

Bach F (1935) The Rheumatic Diseases. London; p 90
Barter R W (1952) *Ann. Rheum. Dis.* **11**, 39
Bennett R A & Copeman W S C (1940) *Brit. med. J.* i, 924
Berglund S (1940) *Nord. Med.* **8**, 2272
Blécourt J J de (1961) In preparation
Bremner J M, Alexander W R M & Duthie J J R (1959) *Ann. Rheum. Dis.* **18**, 279
Bywaters E G L (1950) *Brit. Heart J.* **12**, 101
Edström G (1941) *Acta med. scand.* **108**, 398
Eyquem A, Guyot-Jeanin N & Podliachouk L (1959) *Ann. Inst. Pasteur* **96**, 295
Falls H F (1953) In: Clinical Genetics. Ed. A Sorsby. London; p 282
Franklin E C (1960) *Arthr. & Rheum.* **3**, 16
Geiger J C (1918) *J. Amer. med. Ass.* **155**, 1134
Graaff R de (1960) Proc. I.S.R.A. Symposium on the social aspects of chronic rheumatic joint affections. Amsterdam; p 7
Grossman A J, Leifer P & Batterman R C (1956) *Acta rheum. scand.* **2**, 161
Hope Simpson A E (1940) *Brit. med. J.* i, 830
Jaccoud S (1869) Leçons de Clinique Médicale faites a l'Hôpital de la Charité. 2nd ed. Paris; p 598
Kaufmann & Scheerer (1928) Quoted Falls (1953)
Kellgren J H (1956) *Ann. Rheum. Dis.* **15**, 55
Kellgren J H & Lawrence J S
(1956) *Ann. Rheum. Dis.* **15**, 1
(1957) *Ann. Rheum. Dis.* **16**, 485
Kellgren J H, Lawrence J S & Aitken-Swan J (1953) *Ann. Rheum. Dis.* **12**, 5
Kroner Quoted Falls (1953) as having been quoted by **Weitz** (1936)
Lawrence J S
(1960) *Proc. R. Soc. Med.* **53**, 522
(1961) *Ann. Rheum. Dis.* **20**, 11
Lawrence J S & Ball J (1958) *Ann. Rheum. Dis.* **17**, 160
Lawrence J S & Bennett P H (1960) *Ann. Rheum. Dis.* **19**, 20
Lerner E M, Bloch K J & Williams R R (1960) *Arthr. & Rheum.* **3**, 26
Lewis-Faning E (1950) *Ann. Rheum. Dis.* **9**, Suppl.
Lewis G W (1954) *Rheumatism* **10**, 66
Lloyd K (1960) *Ann. Rheum. Dis.* **19**, 20
Loudon I S L (1953) *Brit. med. J.* i, 1388
Miall W E (1955) *Ann. Rheum. Dis.* **14**, 150
Newman G (1924) *Rep. publ. Hlth med Subj., Lond.* No. 23
Papp J & Tepperberg K (1937) Quoted Falls (1953)
Rep. Minist. Hlth, Lond. (1957) II, 110
Ropes M W, Bennett G A, Cobb S, Jacox R & Jessar R A (1958) *Bull. rheum. Dis.* **9**, 175
Sharp J, Purser D W & Lawrence J S (1958) *Ann. Rheum. Dis.* **17**, 303
Short C L, Abrams N R & Sartwell P E (1952) In: Rheumatic Diseases. Based on Proc. VII Int. Congr. Rheum. Dis. Philadelphia; p 47
Short C L, Bauer W & Reynolds E W (1957) Rheumatoid Arthritis. Cambridge, Mass.
Stecher R M, Solomon W M & Wolpaw R (1952) In: Rheumatic Diseases. Based on Proc. VII Int. Congr. Rheum. Dis. Philadelphia; p 66
Stocks P (1949) Sickness in the Population of England & Wales in 1954. London.
Thymann G (1957) *Acta genet.* **7**, 148
Valkenburg H & Ball J (1961) *Ann. Rheum. Dis.* In press

Section of Radiology

President Frank Ellis MD

Meeting January 20 1961

Pigmented Tumours of the Eye

Mr H B Stallard (*London*)

Surgical Aspects

The subject of pigmented tumours of the eye is of immense importance, for both the fate of an eye and life depend upon correct clinical and pathological assessments, as far as these are possible. In deciding about appropriate treatment, particularly for malignant melanoma of the conjunctiva, it is necessary to exercise wise judgment based on experience that, because of the rarity of these neoplasms, few of us as yet possess.

The supporting tunics of the eye, the cornea and sclera serve in a sense as a physiological and anatomical capsule resistant, for quite a long time, to invasion of a malignant growth from without and, except at the weak sites of emissary vessels and nerves, form for a time a barrier against outward extension of a tumour arising in the uveal tract within the eye. This is of some surgical importance. Except for malignant melanoma of the iris we are still in some ignorance of the variations in natural behaviour of these tumours particularly those occurring in the conjunctiva, ciliary body and choroid and because of this we are often unable to predict the likely course of events.

Malignant Melanoma of the Iris

Undoubtedly our ideas about the treatment of this tumour have the firmest basis. These well-differentiated neoplasms are slow growing, have no karyokinetic figures and when wide iridectomy is performed there has been no instance of local recurrence and no life has been lost from metastases in follow-ups as long as thirty years. Radiotherapy of a malignant melanoma of the iris produces no effective irradiation changes in the tumour cells. Attempts have been made to irradiate malignant melanoma of the iris by inserting radioactive tantalum rods into the anterior and posterior chambers on either side of the neoplasm, a quite unjustifiable, mischievously traumatic and ineffective procedure.

A recent alternative treatment is light coagulation but there is, in doing this, some risk of damage to the cornea and lens. Wide iridectomy is preferable to other methods of treatment.

A nodular malignant melanoma near the iris root may for a time press against the posterior surface of the cornea without infiltrating it but if infiltration seems evident on slit-lamp and corneal microscope examination a disc of corneo-sclera of appropriate size is removed by trephining over the neoplasm, a wide iridectomy is performed and the corneo-scleral defect filled with a corneal graft.

When gonioscopic examination of the filtration angle shows an extension of the iris neoplasm posteriorly into the ciliary body exploration of the extent of this is effected either by reflecting a three-sided scleral flap based posteriorly or by two scleral flaps over the site of the extension. If the extension into the ciliary body is only about 1 or 2 mm and is a thin sheet of cells it is, I think, justifiable to attempt the destruction of this small area by electro-desiccation with a fine diathermy needle and then proceed to wide iridectomy. If, however, the extension into the ciliary body is more than a thin sheet of cells then the more formidable operation of partial cyclectomy is indicated after cutting the iris. To prevent the hazard of vitreous loss Fleiringa's ring is sutured at 8 sites to the epibulbar tissues, and to reduce the risk of intraocular hæmorrhage the growth is circumvallated with penetrating diathermy. The iris is seized with forceps on either side of the neoplasm (Fig 1), is brought into the incision and radial cuts are made on either side from the pupil margin to the iris root. Partial cyclectomy (Fig 2) is effected by a scissors cut passing just anterior to the diathermized area.

A rarity is malignant melanoma of the iris and ciliary body in one eye and of the choroid in the other. The treatment of a large malignant melanoma of the ciliary body, 6 mm or more in diameter, is most unsatisfactory. I have found that both the application of semicircular radioactive ^{60}Co applicators sutured to the sclera and the interstitial insertion of radon seeds have failed. It

is at present too early to assess the result in a patient, aged 31 treated by surface radioactive ^{60}Co six months ago. The neoplasm has shrunk to about a quarter of its original size. Excision of these large neoplasms by partial cyclectomy risks a severe intraocular hæmorrhage and the hazard of vitreous loss. The latter may be prevented by deliberate aspiration of 0·25 ml of vitreous and its replacement at the end of operation.

Malignant Melanoma (Cancerous Melanosis) of the Conjunctiva

The treatment of cancerous melanosis – intra-epithelial malignant melanoma of the conjunctiva – affords a stern challenge which, it seems, may be met only by a combined team of pathologist, radiotherapist and surgeon. These neoplasms are relatively rare, occurring in a proportion of 1 to 40 of intraocular malignant melanomata, a fact that argues for their collection at a centre where one team could treat and follow up.

Opinions about the management of these patients differ from an attitude of *laissez-faire*, still held by a few, to accepting Reese's drastic advice – the mutilating operation of exenteration of the orbit even on diagnosing the so-called pre-cancerous melanosis. There is doubt whether exenteration saves the patient from death by metastases.

The advocates of *laissez-faire*, whose numbers must be dwindling, justify their extreme view by the fact that some of these neoplasms cease to grow and may even disappear spontaneously. It is also a fact that so-called precancerous melanosis may not become malignant for five to ten years and sometimes never. Until we know more about the natural behaviour of these precancerous neoplasms it would seem justifiable to wait and keep them under close observation. It seems futile to take such an intermediate course as advising excision of an unoffending eye still with good vision, for cancerous melanosis does not infiltrate deeply to enter the eye while to leave much of the conjunctiva, as happens with excision of an eye, is inviting local recurrence in the socket.

A partial biopsy of a suspected lesion is unsatisfactory for the pathologist and is, in my opinion, mischievous surgery.

The biopsy should be wide. The lesion should be circumvallated at least 4 to 5 mm wide of its conjunctival limits by diathermy needle coagulation (Fig 3). The dissection is made towards the limbus. An incision is then made about 2 mm beyond the line of corneal infiltration and a lamellar keratectomy performed, the knife being swept from unaffected cornea towards the limbus (Fig 4) whence the block of affected conjunctiva and cornea is removed. If there are small points of infiltration in the sclera these may be touched with a diathermy needle and if more extensive a lamella of infiltrated sclera may be removed.

A small area of denuded sclera and cornea may be covered by undermining adjacent conjunctival flaps and suturing these together. A larger area may require for its cover a free conjunctival graft taken from the upper fornix of one or other eye.

If the lamellar keratectomy is more than 2 mm wide a free-hand lamellar corneal graft is sutured into the defect. When healing is established after this operation prophylactic beta irradiation may be carried out if there is any doubt about a sufficiently wide excision. Large doses of irradiation have blinded the patient from diffuse keratitis and complicated glaucoma.

I have treated a patient with cancerous melanosis by excision of the main mass of growth and by surface diathermy to the multiple islands of pigment cells in the bulbar conjunctiva. Slit-lamp and binocular microscope examination showed that the cell-clumps had shrunk considerably, and there was no recurrence up to the time when she committed suicide, because of domestic unhappiness, five years after this treatment. If cancerous melanosis recurs in the bulbar conjunctiva after excision and beta irradiation a further attempt at surgical removal followed by irradiation, or by the latter alone, would seem justifiable, and exenteration of the orbit kept only for a recurrence which failed to respond to more conservative treatment.

Lids

The surgical treatment of malignant melanoma of the eyelid is wide excision through its full thickness. In the case of a small neoplasm affecting the lid margin or just below this, mobilization of the temporal part of the lid for closure of the surgical coloboma is assisted by orbicularis myotomy at the lateral canthus; and vertical notching of the lid margin is prevented by Wheeler's halving technique.

When the whole lower lid has to be excised, a temporary tarsorrhaphy is done and a delayed bridge pedicle is raised and lined with a free conjunctival or buccal mucosal graft. One week later this is swung down into place.

When the whole upper lid is excised immediate cover of the eye is effected by splitting the lower lid, mobilizing the tarsal plate and suturing to this the levator palpebræ superioris muscle and

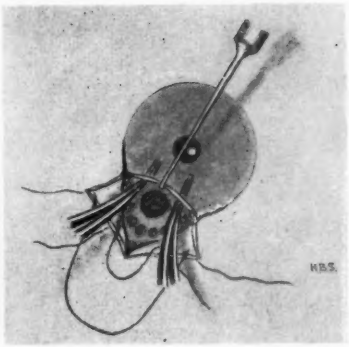


Fig 1 *Iridocyclectomy. Scleral flaps reflected, cornea raised by hook. Iris seized with forceps on either side of neoplasm*

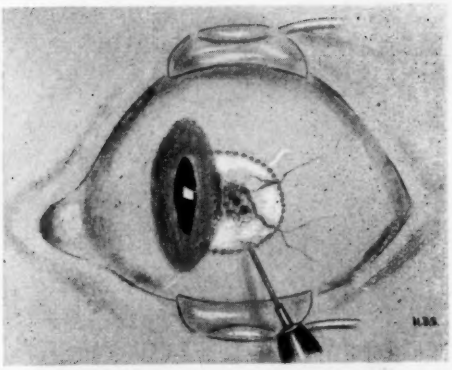


Fig 3 *Malignant melanoma of conjunctiva and cornea. Circumvallation with a diathermy needle*

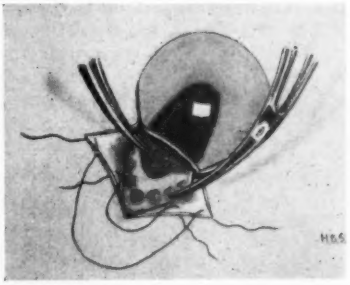


Fig 2 *Partial cyclectomy. The malignant melanoma in the ciliary body has been circumvallated with diathermy. Radial cuts in the iris have been made on either side of the neoplasm. Scissors incision through ciliary body*

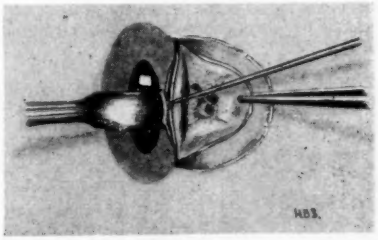


Fig 4 *Lamellar keratectomy*

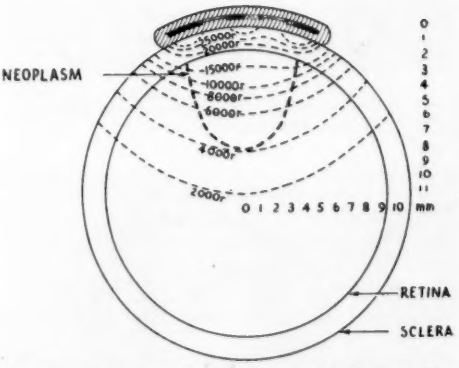


Fig 5 *Isodose curves for a* 10 *mm active diameter disc loaded with* 1·46 *mc* ^{60}*Co applied for seven days*

the conjunctiva of the upper fornix. A bridge pedicle of skin is brought down and into the defect thus left a full thickness skin graft is placed.

Choroid

We are sometimes faced with the tragedy o malignant melanoma of the choroid in an only eye, or where the other eye is grossly diseased or too amblyopic to be of use. Indeed the vision in the affected eye may be very good and the neoplasm small. In such circumstances it seems justifiable on clinical results to date to try irradiation by bringing the radioactive source as close as possible to the neoplasm and striking it with a dose which we hope will be lethal to the neoplasm and safe for the eye. The results of irradiation seem to be better when the neoplasm has not penetrated Bruch's membrane, in females and in the young.

As most of these neoplasms have a circular base, radioactive discs which conform to the

Fig 6 *Fundus painting of graticule shadow projected by ophthalmoscope over malignant melanoma of choroid above optic disc*

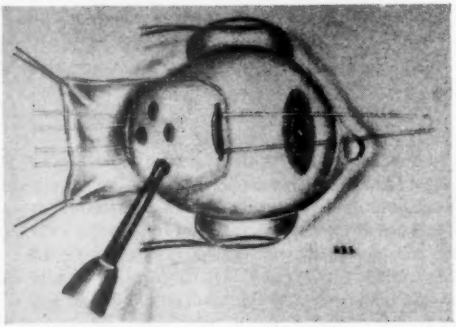


Fig 7 *Site of neoplasm marked on exposed sclera with either katholysis or diathermy*

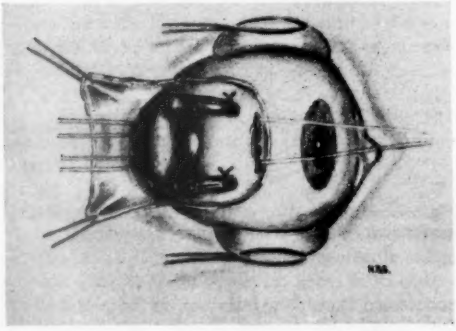


Fig 8 *Radioactive disc sutured to sclera precisely over site of neoplasm*

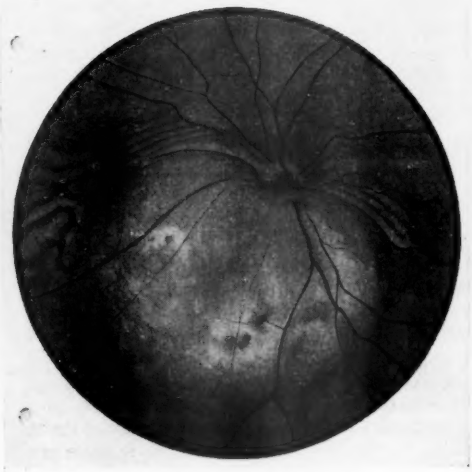


Fig 9A

Fig 9B

Fig 9 A, *malignant melanoma, nasal side of optic disc. Left eye before irradiation.* B, *after irradiation*

curvature of the sclera have been used, of appropriate size for the radioactive element to overlap the periphery of the neoplasm by at least 1 mm. The loading has been designed to give even isodose curves in a lenticular or hemispherical tumour arising from a curved surface (Fig 5).

Crescentic applicators are used when the neoplasm is adjacent to the optic disc, the concavity of the crescent embracing the optic nerve.

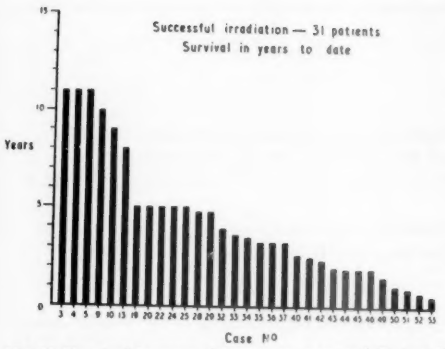


Fig 10 *Survival in years.* 31 *patients successfully irradiated to date*

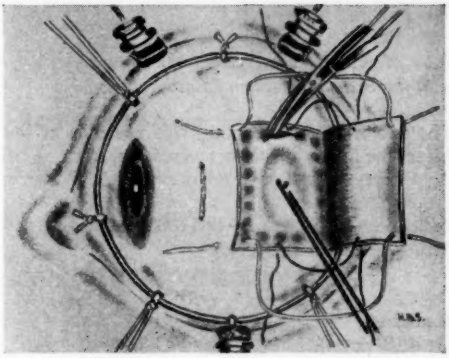


Fig 11 *Excision of malignant melanoma of choroid through diathermy circumvallation*

The size of the neoplasm may be assessed with fair accuracy by a graticule projected on to the fundus by an ophthalmoscope (Fig 6). At operation the site of the neoplasm is marked by either katholysis punctures or diathermy (Fig 7), and confirmed by ophthalmoscopic examination. The radioactive applicator is applied precisely over the marked site and the holes in its lugs are marked with gentian violet. At these marks scleral sutures are inserted and then are brought through the holes in the lugs to secure the applicator to the sclera (Fig 8).

Fig 9A is a fundus painting of a malignant melanoma on the nasal side of the optic disc, which after irradiation has been for twelve years a flat scarred area (Fig 9B).

The results in a series of 59 patients show that 31 of these seem to be successful to date; 2 were successful but died of intercurrent disease, 1 nineteen years after irradiation; 1 has become blind; 11 have had the eye excised because the neoplasm was not completely destroyed; in 11 the result is still uncertain; and 3 in whom the growth was far advanced have died of metastases. Fig 10 shows the survival in years to date of the 31 successes. It is of course improper to claim a five-year survival as a cure, for patients have been known to die of melanotic metastases twenty years after excision of an eye, indeed Chisholm (1953) quotes a case of thirty-six years' survival before clinical evidence of metastases occurred.

Rarely it may be justifiable to attempt local excision of a neoplasm in an only eye when irradiation has failed. This formidable operation is done through a lamellar scleral flap trap-door placed over and wide of the base of the neoplasm. Diathermy circumvallation should effect hæmostasis in the line of resection (Fig 11). Surprisingly it is possible to achieve removal of the neoplasm without loss of vitreous. Post-operative intraocular hæmorrhage may spoil the result.

Acknowledgment: I thank Mr F S Stewart and Mr G Innes for much help and advice in the design of the radioactive cobalt applicators.

BIBLIOGRAPHY

Benjamin B, Cumings J N, Goldsmith A J B & Sorsby A (1948) *Brit. J. Ophthal.* **32**, 729
Cade S (1952) Malignant Disease and its Treatment by Radiotherapy. 2nd ed. Bristol; Vol. 4
Chisholm J F (1953) *Amer. J. Ophthal.* **36**, 61.
Green H W & Whiteley H J (1952) *Brit. med. J.* ii, 538
MacRae A (1953) *Trans. ophthal. Soc. U.K.* **73**, 3
Moore R F (1930) *Brit. J. Ophthal.* **14**, 145
Pack G T, Perzik S L, & Scharnagel I M (1947) *Calif. Med.* **66**, 283
Stallard H B
(1933) Radiant Energy in the treatment of certain Eye Diseases. (*Brit. J. Ophthal.* Monograph Suppl. No. 6). London.
(1949) *Trans. ophthal. Soc. U.K.* **69**, 293
(1961) *Ann. R. Coll. Surg. Engl.* In press.
Watzold P (1930) *v. Graefes Arch. Ophthal.* **124**, 139

Professor Norman Ashton (*London*) described the pathology of melanomas of the uvea, their histology, prognosis and histogenesis. He also discussed pigmented tumours of the eyelids and conjunctiva with special reference to cystic nævi, juvenile nævi and blue nævi, and gave an account of intra-epithelial melanoma of the conjunctiva. His subject matter is summarized elsewhere.[1]

[1] **Ashton N** (1957) In: Cancer. Ed. R W Raven. London; **2**, 599

Dr M Lederman spoke on **Radiotherapy of Malignant Melanomata of the Eye.** A full account of his paper will be found in *Brit. J. Radiol.* 1961, **34**, 21.

Joint Meeting December 16 1960
with the British Institute of Radiology

The subject of the meeting was **Diseases of the Liver**; the following papers were read:

Indications for Radiology and Radiotherapy
Professor Sheila Sherlock

Radiology
Dr W B Young

Radio-isotopes in Investigating Liver Function
Mr H S Williams and Dr S Shaldon

Recuperation of the Liver
Professor Sir Roy Cameron

The papers will be published in the *British Journal of Radiology*.

Joint Meeting December 17 1960
with the Faculty of Radiologists
at the Royal College of Surgeons
Lincoln's Inn Fields London

The subject of the meeting was **Tumours of the Mandible**; the following papers were read:

Pathology
Professor R B Lucas

Radiology
Dr F L Ingram

Prosthetic Aspects
Mr H P Cook

Surgery
Sir Stanford Cade

Radiotherapy
Professor B W Windeyer

The papers will be published in *Clinical Radiology*.

Section of Anæsthetics

President R F Woolmer VRD FFA RCS

Meeting March 3 1961

Angiocardiography

Dr E R Lester (*London*)

Anæsthetic Problems and Techniques

Angiocardiography is employed to visualize abnormalities of the heart, great vessels or pulmonary vasculature, often prior to cardiac surgery. In the earlier cases contrast medium was injected directly into a peripheral vein, but with the advent of selective angiocardiography a catheter is inserted through a peripheral vein to the right side of the heart, where X-ray screening and intracardiac manometry assist in placing its tip in the desired position. This may be a pulmonary artery or the pulmonary trunk, the right chambers of the heart, or the venæ cavæ. A calculated volume of contrast medium is rapidly injected and simultaneously a series of films are exposed in two planes. The contrast is injected at about 25 ml per second and the films are exposed over several seconds. The average duration of anæsthesia is thirty to forty-five minutes.

All procedures in the X-ray department present problems to the anæsthetist. These include the explosion hazard, the darkness during screening, the alterations in positioning of the patient, the clutter of wires and machinery and the dangers of radiation to the anæsthetist himself. Moreover, the emergency facilities, such as suction and adequate nursing assistance, which the anæsthetist takes for granted in the theatre suite, may not be readily available. In addition, patients for angiocardiography are often poor anæsthetic risks. The majority have severe cardiac disease and may be cyanosed, dyspnœic and have chronic chest infections. They require to be treated with the same respect as patients for major cardiac surgery and will react badly to anoxia or relatively minor circulatory upsets.

Although in the older patient this investigation may be satisfactorily performed under sedation combined with local anæsthesia, at the Middlesex Hospital general anæsthesia is now employed for nearly all cases. Local infiltration is of value, however, even in cases under general, as it permits a lighter plane of anæsthesia and helps to prevent venospasm. The majority of children require a general anæsthetic as the unfamiliar environment of the X-ray department, the period of darkness during screening, the necessity for all but the smallest to hold their breath during exposure of the films, the frightening noise of the Elema machine and the possible unpleasant effects of the contrast medium all demand considerable stoicism from even a well-sedated, but still conscious, child. Any disturbance during and for some seconds after the injection can render the whole procedure valueless.

Although over-sedation must be avoided, adequate premedication is essential as emotional upsets increase oxygen requirements and release endogenous adrenaline: this may be reflected in ECG changes, which may persist for several minutes. Moreover, if induction is not smooth, due to crying, coughing or straining, the associated rise in intrathoracic pressure may result in dangerous anoxia from embarrassment of the pulmonary circulation, especially in patients with a right-to-left intracardiac shunt. Full oxygenation and minimal alteration in circulatory dynamics are required throughout the anæsthetic procedure. Hypotension is equally dangerous, again, particularly in patients with a right-to-left shunt and will also upset the radiologist's calculations for timing the exposures. As a rule, the deeper the plane of anæsthesia the greater the fall in blood pressure during the transient period of vasodilatation, which occurs after the injection of contrast media (Howarth 1950).

In angiocardiography, a relatively large volume (1 ml/kg) of hypertonic contrast medium is injected rapidly into a vein or into the right side of the heart in patients suffering from cardiac or pulmonary disease. It is, therefore, hardly surprising that there is a price to pay. At the Middlesex Hospital there have been 7 deaths in 472 investigations, a mortality of 1·5%, which compares not unfavourably with the published figures for other centres, which vary from 0·2 to 4·0% (Table 1). In the report of Dotter & Jackson

Table 1
Reported mortality for angiocardiography

Authors	*No. of investigations*	*No. of deaths*	*Mortality rate %*
Campbell & Hills (1950)	50	2	4
Carnegie (1951)	172	4	2·3
Goodwin *et al.* (1949)	118	2	1·7
Reynolds (1953)	73	1	1·4
McAfee (1955)	782	8	1
Rowe *et al.* (1956)	249	5	2
Dotter & Jackson (1950)	6,824	26	0·38
U.S.A. & Canada	5,961	18	0·3
Sweden	450	1	0·2
Great Britain	413	7	1·7
The Middlesex Hospital (1960)	472	7	1·5

Table 2
Fatalities in the Middlesex Hospital series

Serial No.	*Age (years)*	*Cyanosis*	*Pulmonary hypertension*	*Anatomy*
112	4½	+	–	Pulmonary stenosis. Auricular septal defect
126	16	+	–	Pulmonary stenosis. Auricular septal defect
236	4½	–	+	Ventricular septal defect
259	29	–	+	Mitral stenosis. Aortic incompetence
268	65	–	–	Systemic hypertension. ? Pulmonary arteriovenous fistula
292	24	–	+	Primary pulmonary hypertension
429	8	+	+	Tricuspid atresia. Auricular and ventricular septal defects

(1950), who by a postal questionnaire collated the figures from the majority of centres performing this investigation, the high mortality in Great Britain is explained by the fact that the majority were 'bad-risk' cases of congenital heart disease, whereas in the U.S.A., Canada and Sweden a large number of less ill patients with acquired heart disease were also investigated.

Table 2 shows the fatalities in the Middlesex Hospital series. Fatalities occurred in all age groups from 4½–65 years. Three of the cases were cyanosed, 4 had pulmonary hypertension and 2 pulmonary stenosis.

Table 3 shows that three types of contrast media were involved in the 7 fatalities. Sensitivity tests to them were negative. The first 2 patients who died were in the early part of the series and both received two injections of contrast medium resulting in a total dosage of two and a half times the dose by weight used to-day. The site of injection varied from an arm vein to the pulmonary trunk and the time for an adverse reaction to manifest itself after an injection of contrast was within two hours in 6 of the 7 cases.

There were also 12 patients who had severe non-fatal reactions, which included one or more of the following: vomiting, apnœa, bronchospasm, hæmaturia, hæmatemesis, hypotension, circulatory collapse and prolonged unconsciousness. In the earliest cases, when basal narcosis only was employed, 2 children became apnœic and pulseless after one injection of diodone. Two of the fatal cases and 4 with severe reactions received two injections of contrast. Fifty-two cases of multiple injections are recorded and the total reaction rate in these cases was 11·5%, which compares unfavourably with the rate of 2·8% for single injections, although it must be taken into account that patients receiving multiple injections usually had the more complicated cardiac abnormalities. However, this is now only of historic interest, as multiple injections are unnecessary when a biplane machine is available, which allows films to be exposed simultaneously in two planes at right angles. All these non-fatal reactions occurred after a negative sensitivity test, but in one patient's records no note has been made with regard to the test. In another patient there was a mild reaction to the test-dose, which was attributed to apprehension; the test was repeated under anæsthesia without any reaction, but the child developed apnœa and bradycardia when the full injection was given and did not fully recover for twenty-four hours.

Intravenous pethidine or *d*-tubocurarine, or both, were given in 6 patients who died or developed severe reactions. This may support the hypothesis that histamine release is an important factor in producing these reactions (Mann 1961).

Table 3
Details of contrast medium in fatal cases in the Middlesex Hospital series

Serial No.	*Contrast*	*Sensitivity test*	*No. of injections*	*Total dose (ml/kg)*	*Site of injection*	*Interval from injection to reaction*
112	70% diodone	Negative	2	2·5	Arm vein	10 min after 2nd injection
126	70% diodone	Negative	2	2·8	Arm vein	12 min after 2nd injection
236	70% Diaginol	Negative	1	1·5	Right atrium	60 minutes
259	70% Diaginol	Negative	1	1·0	Superior vena cava/right atrium junction	5 minutes
268	70% Diaginol	Negative	1	1·0	Pulmonary trunk	?
292	70% Diaginol	Negative	1	1·3	Superior vena cava	1 minute
429	85% Hypaque	Negative	1	1·3	Right atrium	120 minutes

Three further cases had to be abandoned before injection of contrast and are not included in the series. One developed uncontrollable tachycardia and another severe cardiac arrhythmias, which could not be abolished by altering the position of the catheter or changing the anæsthetic. The third developed persistent heart block.

Since Cope reviewed the literature in 1953, several anæsthetic techniques for angiocardiography have been described (Gibson 1953, Barran 1953, Duncalf & Thompson 1956, Mehta 1959). Three main techniques have been employed for the 380 patients who received a general anæsthetic in the series of 472 at The Middlesex Hospital. The first two methods have been mainly replaced by the third, but are still occasionally used by individual anæsthetists. Thus the last death, which occurred in 1960, was in a patient who was anæsthetized by the first technique. Only in one case can the anæsthetic technique be suspected of directly contributing to death. This patient required reversal of curarization and reacted to neostigmine with severe bradycardia followed by cardiac arrest, in spite of adequate atropine, full oxygenation and apparent normocarbia. Twenty-five cases were anæsthetized by a variety of miscellaneous methods, in which logical reasons for their choice were not apparent, but the remainder can be classified under 3 headings:

The First Technique was described by Cope in 1953. Children were premedicated with atropine by injection one hour prior to angiocardiography, followed by rectal thiopentone, 1 g/50 lb (44 mg/kg) body weight, thirty-five minutes later. Children over 50 lb in weight and adults were given papaveretum and either hyoscine or atropine. This premedication for the smaller children has stood the test of time and has been employed throughout the series. For the older patients papaveretum has been replaced by pethidine and promethazine. The latter drug is of value in counteracting minor allergic reactions.

In Cope's technique induction of anæsthesia is with intravenous thiopentone and maintenance with nitrous oxide, oxygen and trichlorethylene. The oxygen percentage is kept at 30% or more and the trichlorethylene concentration kept minimal to avoid cardiac irregularities. 1% procaine is infiltrated in the skin and perivenously prior to insertion of the catheter. Anæsthesia is deepened with additional thiopentone before the injection of contrast to avoid undesirable reflexes, and the lungs inflated with 100% oxygen. After injection of contrast no further anæsthetic agents are required, as the removal of the catheter and repair of the vein and skin are rapidly accomplished. Recovery of reflexes may be delayed, due to the additional thiopentone given late in the procedure, but the children are quiet post-operatively and sleep for up to three hours. The patient is returned to the ward in the lateral position, the foot of the bed raised and oxygen delivered by mask.

The Second Technique was employed after the introduction of suxamethonium and the acceptance of Barran's recommendation in 1953 for total paralysis during the injection of contrast to prevent adverse reactions. The majority of cases were induced with intravenous thiopentone and intubated with a cuffed oral endotracheal tube under suxamethonium after spraying the larynx with lignocaine. Anæsthesia was continued with nitrous oxide and oxygen; on recovery from the suxamethonium, *d*-tubocurarine was given and ventilation controlled. At the end of the procedure reversal of the curarization was necessary with neostigmine preceded by atropine.

The advantages of this technique are the complete protection of the upper airway, the control of ventilation at all times, and the protection against untoward reactions to contrast media that the relaxants appear to provide. Recovery is rapid, due to the light plane of anæsthesia. The disadvantages include the use of 2 relaxants with different modes of action, and the delay between recovery from suxamethonium and the onset of the action of curare, which may result in coughing or bronchospasm, despite the application of lignocaine to the larynx. The presence of the endotracheal tube in the larynx may itself predispose to arrhythmias. Continuous paralysis and control of ventilation are not necessary, and may upset circulatory dynamics. Finally, a diseased heart, which has endured the presence of a catheter followed by an injection of contrast, may react badly to neostigmine even if anoxia and hypercarbia are avoided (Riding 1960). As already mentioned, neostigmine probably contributed to the fatal outcome in one of our cases.

The Third Technique has been used for the majority of patients over the last two years and marks a return to the principles enunciated by Cope, but using halothane instead of trichlorethylene, and suxamethonium to ensure control during the injection, in preference to thiopentone. Premedication is as already described, induction is with thiopentone or, if no suitable vein is available, with nitrous oxide, oxygen and halothane. Maintenance of anæsthesia is initially with nitrous oxide, and at least 30% oxygen and minimal halothane vaporized from a Fluotec, and delivered from a semi-closed circle absorption system to the smallest possible face-piece, which is carefully fitted to the patient with Clausen's head-harness. A light plane of anæsthesia is maintained and the stimulus of skin incision covered by local anæsthetic.

Before the lights are turned off for screening, the nitrous oxide is discontinued and anæsthesia maintained with an oxygen-halothane mixture. A hand is kept on the reservoir bag so that any fault in the oxygen supply soon becomes apparent. The expiratory valve is set to blow off audibly. The anæsthetist need not expose himself to radiation, yet still has three guides to his patient's condition during the period of darkness: namely, the feel of the reservoir bag, the sound of the expiratory valve and the ECG monitor.

When the catheter is in position the patient is moved under the Elema machine. The halothane is turned off and suxamethonium given. A final check on the patient's position is made following the muscle fasciculations. Manual inflation with pure oxygen continues until the moment of injection of contrast, when ventilation ceases and light pressure is applied to the reservoir bag to depress the diaphragm. Ventilation with oxygen is continued while the catheter is withdrawn and the skin sutured. Spontaneous respiration and protective reflexes return rapidly. The patients are placed in the lateral position and oxygen administered by mask. In view of past experience of the occurrence of delayed reactions, these patients are closely observed for two hours.

Some anæsthetists modified this technique by omitting halothane. This was done on 48 occasions, usually in children who had had rectal thiopentone, when it was found possible to maintain adequate anæsthesia solely with nitrous oxide and oxygen. While with this method the essential extra oxygen may easily be given after the suxamethonium and during the injection of contrast, this is less easy during the preliminary catheterization which may last for thirty minutes. As this oxygen is equally desirable during this period, the halothane technique already described is preferred and this method has been successfully employed for 176 recent cases.

The possible disadvantages of halothane are respiratory depression, especially if premedication is excessive (Bryce-Smith & O'Brien 1957), hypotension and cardiac arrhythmias. The latter may be exacerbated by hypercarbia or inadequate atropinization (Johnstone 1956, Black *et al.* 1956). For these reasons light halothane anæsthesia is desirable and is one reason for avoiding intubation, as a deeper plane of anæsthesia is then required. Nevertheless, if it proves difficult to maintain a clear airway, we do not hesitate to pass an endotracheal tube, and this is also done to reduce dead space in small patients. Suxamethonium may be used to facilitate intubation, but introduces the possible hazard that cardiac arrhythmias may follow the second injection of this drug (Lupprian & Churchill-Davidson 1960). In fact we have not seen any alarming reactions of this kind either after the first (Craythorne *et al.* 1960) or subsequent doses of suxamethonium. The vast majority of arrhythmias have been related to manipulations of the catheter and have been abolished by altering its position. However, injection of contrast directly into the right heart almost invariably produces a short run of ventricular extrasystoles. We have not recognized any superimposed change attributable to suxamethonium.

Table 4
Anæsthetic techniques at the Middlesex Hospital

Technique	*No. of cases*	*No. of deaths*
Trilene + thiopentone (1948–54)	82	3
Intubation + relaxants (1954–57)	49	4
Halothane + suxamethonium (1958–60)	176	Nil
Nitrous oxide, oxygen & suxamethonium (1958–60)	48	Nil
Miscellaneous techniques (1948–58)	25	Nil

It would appear that in practice the benefits of halothane and suxamethonium outweigh the theoretical disadvantages of these drugs. The latter provides effective control of undesirable reflexes, while the former ensures smooth induction and maintenance of anæsthesia with the desirable high concentration of inspired oxygen.

Table 4 summarizes our use of the three anæsthetic techniques. Each had a period during which it was most commonly employed. The number of patients anæsthetized by each method is shown and the deaths that occurred. It must be stressed again, however, that in only one case could the anæsthetic technique be suspected of directly contributing to death, this being the adverse response to neostigmine already described.

Nevertheless, although the satisfactory results offered with this last technique are most gratifying, anæsthesia is concerned with only one aspect of the risks in angiocardiography. The adverse effects of contrast media, the radiological techniques, and the type of cardiac lesions are of equal importance.

REFERENCES

Barran D A N (1953) *Anæsthesia* **8**, 191
Black G W *et al.* (1956) *Brit. J. Anæsth.* **31**, 238
Bryce-Smith R & O'Brien M D (1957) *Proc. R. Soc. Med.* **50**, 193
Campbell M & Hills T H (1950) *Brit. Heart J.* **12**, 65
Carnegie D M (1951) *Brit. med. J.* i, 1230
Cope D H (1953) *Brit. J. Anæsth.* **25**, 212
Craythorne N W B *et al.* (1960) *Anesthesiology* **21**, 465
Dotter C T & Jackson F S (1950) *Radiology* **54**, 527
Duncalf D & Thompson P W (1956) *Brit. J. Anæsth.* **28**, 450
Gibson J B (1953) *Anæsthesia* **8**, 269
Goodwin J F, Steiner R & Wayne E J (1949) *Brit. Heart J.* **11**, 279
Howarth S (1950) *Brit. med. J.* ii, 1090
Johnstone M (1956) *Brit. J. Anæsth.* **28**, 392
Lupprian K G & Churchill-Davidson H C (1960) *Brit. med. J.* ii, 1774
Mann M R (1961) *Proc. R. Soc. Med.* **54**, 473
McAfee J G (1955) *Amer. J. med. Sci.* **229**, 549
Mehta M (1959) *Anæsthesia* **14**, 43
Reynolds G (1953) *Brit. Heart J.* **15**, 74
Riding J E (1960) Second World Congress of Anesthesiologists, Toronto, Paper 138
Rowe G G *et al.* (1956) *Circulation* **13**, 896

Dr M Regina Mann (*London*)

The Pharmacology of Contrast Media

In this review the term contrast media refers to the water-soluble organic iodine compounds given by intravascular injection. The main actions of contrast media can be summarized as follows:

(1) *Peripheral Vasodilatation and Consequent Fall of Blood Pressure*

The fall does not occur immediately but is delayed for up to 20 seconds after the injection. Vasodilatation results from an action on the vessel wall and on intra-arterial injection a brief vasoconstriction precedes the dilatation. A tachycardia occurs [2, 20, 32, 34, 37, 40, 44, 69, 77, 80, 87, 92, 102].

(2) *Angiotoxic Action*

The mildest form of injury is an increased capillary permeability. This has been demonstrated in animals in the cerebral vessels by the use of staining techniques, microscopy and by the rise of pressure and protein content of the C.S.F. The severity of these changes parallels the degree of disturbance of cerebral function as shown on the EEG [4, 10, 11, 14–17, 32, 105]. The mild form of injury has also been demonstrated in the kidney, when microscopy shows that the glomeruli are hyperæmic and an albuminous exudate is present in Bowman's capsule [42]. Repeated injections and higher concentrations of medium have greater toxic effects on the vessels. When moderate the injury is demonstrable microscopically as vasodilatation, congestion, ball-shaped perivascular hæmorrhages and parenchymal œdema. When severe it amounts to a hæmorrhagic infarct visible to the naked eye. Such lesions have been produced in animals in the brain, spinal cord and kidney [11, 42, 54].

Angiotoxic damage has been noted in man; in the brain, following cerebral angiography and thoracic aortography [5, 96, 100], and in the lungs, following selective angiocardiography. In this last examination concentrated medium is injected directly into the pulmonary circulation. The lesions are similar to those described in the central nervous system, i.e. pulmonary œdema, hæmoptysis and consolidation of the lung [8, 19, 51, 87, 89, 95]. Angiotoxic damage has also been noted in the kidney, pancreas, adrenals, small intestine, colon and rectum following abdominal aortography [41, 43, 52, 83, 90].

(3) *Side-effects*

This term in relation to contrast media has come to be applied to the subjective feelings of the patient and the allergic responses observed. A patient may experience a single effect or a number of effects. These are grouped where possible according to their ætiology.

Subjective reactions: (*a*) Flushing, sensation of warmth and headache (effects associated with vasodilatation). (*b*) Weakness, faintness, dizziness and tinnitus (effects associated with a fall of blood pressure). (*c*) Metallic or foreign taste in the mouth, salivation, nausea, retching, vomiting and colicky abdominal pain which may be situated in the epigastrium or lower abdomen and can be associated with a desire to defæcate or urinate, or actual incontinence of fæces or urine (alimentary effects mainly due to smooth muscle stimulation). (*d*) Pain in the arm or shoulder (stimulation of venous smooth muscle). (*e*) coughing.

Allergic reactions: (*a*) Urticaria, angioneurotic œdema, laryngeal œdema and rhinorrhœa (effects due to an increased capillary permeability). (*b*) Lacrimation (stimulation of the lacrimal gland). (*c*) Sneezing. (*d*) Pruritus, tingling sensation, 'pins and needles' and numbness (effects associated with involvement of peripheral nerves). (*e*) Laryngeal spasm and bronchospasm; all degrees of bronchospasm occur from a sensation of tightness in the chest or wheezing to a frank attack of asthma (effects due to smooth muscle stimulation). (*f*) Anaphylactoid shock. In this response the patient collapses with a weak or impalpable pulse, low or unrecordable blood pressure, ashen pallor and sweating. He may become unconscious and there can be respiratory difficulty or arrest accompanied by cyanosis. Sometimes one of the other allergic manifestations, e.g. urticaria, accompanies the collapse [1, 3, 13, 22, 28, 31, 35, 47, 50, 55, 60–62, 64–66, 68, 81, 84, 85, 94, 97, 101, 106].

Evidence for Release of Histamine by Contrast Media

One can recognize in the actions of contrast media and their side-effects the characteristics of a histamine-releasing agent. Such an agent is not protein in nature, and releases histamine on first contact, prior sensitization being unnecessary. To be placed in this category a compound must fulfil certain requirements: (1) It must produce the delayed depressor response [30, 53, 71].

(2) It must have certain structural criteria. The possession of basic groups by a compound predisposes it to histamine-releasing activity. If there are two or more basic groups they must be sufficiently separated on an aliphatic or aromatic scaffold. If there is only one basic group the compound must have another polar group attached to the aromatic ring [53, 71]. Examination of the structural formulæ of contrast media shows that diodone, diatrizoate and diprotrizoate are dibasic aromatic compounds and belong to the first

category; Uroselectan, iodoxyl and acetrizoate are monobasic compounds with the basic group attached to substituted aromatic rings, and belong to the second.

(3) It must produce the triple response on injection into human skin [71]. This is evidence of the compound's histamine-releasing activity in man, important because histamine-releasing agents show species specificity. Contrast media produce the triple response, which has been used as a sensitivity test [1, 61, 82, 94].

Contrast media produce the delayed depressor response and the triple response and possess the necessary structural criteria. They can be placed correctly in the group of substances which are histamine-releasing agents.

That histamine is released on injection of contrast media is illustrated more vividly perhaps when the effects of contrast media are compared with those of other known histamine liberators, and with the effects of histamine itself. The liberators chosen for this comparison are the organic arsenicals, the organic diamidines (formerly used in the treatment of certain tropical diseases) and Compound L1935, a substituted butylamine used in human experimental pharmacology [46, 48, 49]. Table 1 shows how similar are the main side-effects of these substances; histamine and Compound L1935 appear to produce fewer side-effects than the others but it must be recalled that there was a limit to the dose of these substances as they were given to human volunteers during pharmacological experiments. When a substance is used therapeutically and histamine release is coincidental this consideration does not apply.

Relevant Actions of Histamine

Injected intravenously (I.V.) in small doses histamine causes flushing of the face, sensation of heat and a salty, electric or metallic taste in the mouth. Higher doses cause the flush to spread and tachycardia, nausea and vomiting to occur. With relatively large doses there is a marked fall of blood pressure with sensation of weakness, pronounced tachycardia and intense headache [103, 104]. On injection of histamine urticaria, angioneurotic œdema, pruritus and paræsthesiæ do not occur because these phenomena are caused only by endogenous release of histamine.

The main actions of histamine with which we are concerned are: (1) Dilatation of capillaries and arterioles. (2) Increased capillary permeability. (3) Stimulation of smooth muscle. (4) Stimulation of glands.

Vasodilatation gives rise to flushing, sensation of warmth and headache and to the fall in blood pressure with its attendant sense of weakness, faintness and dizziness. An increased capillary permeability underlies urticaria, angioneurotic œdema, laryngeal œdema and rhinorrhœa. Stimulation of the smooth muscle of the intestine, stomach and bladder gives rise to colic, vomiting, desire to defæcate or urinate or actual incontinence of fæces or urine. When the human bronchial chain is suspended in a bath it responds readily to histamine and its sensitivity is approximately the same as that of the guinea-pig tracheal chain [91]. Injected into man in safe doses, histamine does not cause broncho-constriction in normal subjects but it does in those who suffer from asthma, cardiac asthma and patients with chronic bronchitis and emphysema [23, 24, 38, 103]. This effect is not confined to histamine but occurs with other broncho-constrictor substances, e.g. inhalational anæsthetics, 5-hydroxytryptamine and acetyl-beta-methylcholine [25, 38, 39, 56, 67]. Stimulation of glands by histamine underlies lacrimation, salivation and increased bronchial secretion. This effect also underlies the release of amines from the adrenal gland which causes or accentuates the tachycardia so often noticed. Dangerous release of adrenal amines can occur in a patient with phæochromocytoma, causing a hypertensive crisis and even death from adrenaline shock. Two deaths have been reported in such patients after the use of contrast media for abdominal aortography [2, 43, 90].

Properties of Histamine-releasing Agents and Their Relation to the Effects of Contrast Media

Dosage: An increase in the dose of histamine-releasing agent leads to an increase in the amount of histamine liberated. This is measured in animals

Table 1

Comparison of effects of contrast media, histamine and known histamine liberators

Reaction	*Contrast media*	*Organic arsenicals*	*Organic diamidines*	*Compound L1935*	*Histamine*
Flushing, headache, warmth	+	+	+	+	+
Fall in blood pressure, tachycardia	+	+	+	+	+
Nausea, vomiting	+	+	+	+	+
Abdominal pain	+	+	+	+	–
Unconsciousness					
salivation, incontinence	+	+	+	–	–
Weakness, foreign taste	+	–	–	–	+
Faintness	+	–	+	–	–

by the extent of the fall in blood pressure. A small dose causes a transient fall in blood pressure; with larger doses the fall is more prolonged and severe [45, 53]. In man the amount of histamine liberated is indicated by the number and severity of the reactions. This has been shown experimentally using Compound L1935 [46]. This relationship is also seen with contrast media; e.g. when diodone is used for intravenous urography, in general only a proportion of the patients are affected by reactions considered to be relatively mild. In angiocardiography, when larger doses are employed, all the patients suffer a moderately severe reaction.

Self-potentiation: By this term is meant the increased response to a second injection given a short time after the first. This is a characteristic of histamine liberators. The transient fall in blood pressure produced by a small dose can be reproduced only if ten minutes or longer are allowed to elapse before giving the second injection. Otherwise it evokes a bigger response than the first and a dose which was originally below threshold produces a large effect when repeated [53, 70].

Self-potentiation is a feature of contrast media. The dangers of repeating an injection without allowing a sufficient interval between them are well recognized clinically. There are many reports of patients who tolerated the first injection of contrast medium but suffered a severe and often fatal reaction when it was repeated [27, 59, 73, 87, 98].

Threshold dose and sensitivity tests: There is a threshold below which histamine is not released by histamine liberators [53]. An intravenous injection of 1 ml of contrast medium is below threshold in the majority of the population and consequently bears no relation to the amount of histamine which will be released when the full radiographic dose is given. Thus the preliminary injection of a small dose of medium is valueless as a test. However, it is still probably worth retaining for the following reason. There is an individual variation in the response to histamine liberators and a small proportion of the population possess an idiosyncrasy, i.e. an overwhelming release occurs with a small dose. The reason for this idiosyncrasy is not known. It has been noted with contrast media and patients have died as the result of small quantities of medium, even 1 ml, given as a test dose [7, 18, 26, 33, 72, 74, 75, 93, 107]. If a patient has this idiosyncrasy and is given prompt treatment he may recover if only 1 ml of contrast medium has been given, whereas it may prove impossible to reverse the effects of a full radiographic dose.

Other sensitivity tests: Histamine is not released when applied to a mucous membrane. Therefore the conjunctival and oral tests cannot be expected to give any information. Skin testing has been tried with contrast media and with other histamine liberators (e.g. muscle relaxants) and a very limited correlation obtained between the size of the response and the extent of the general reaction [1, 12, 61, 94, 99]. The triple response fails as a test because it does not predict which patients will have a severe reaction. The probable reason for this is that different organs in the body have different amounts of releasable histamine and different sensitivities to a particular liberator [29, 58, 78, 79]. The skin can give no indication of the content and sensitivity of the other organs of the body which participate in histamine release on I.V. injection.

Allergic subjects: Patients who suffer from allergic diseases are more liable than normal subjects to have a reaction from contrast media [1, 22, 50, 60, 85, 94, 107]. The reason for this is that allergic patients have a higher content of histamine than normal in their 'sensitive' organ (the bronchi in asthmatics, the nasal mucous membrane in sufferers from hay fever) [6, 86]. An asthmatic is thus doubly handicapped. He not only has a greater quantity of histamine available for release, but he is more sensitive to its bronchoconstrictor action than is a normal subject.

Release of other substances: Other substances in addition to histamine may be released, e.g. 5-hydroxytryptamine and the vasodepressor and smooth-muscle-stimulating polypeptides, slow reacting substance (S.R.S.) and bradykinin. These accentuate and prolong the hypotensive action of the histamine liberator [9, 36, 53, 70, 88]. A substance similar to bradykinin and S.R.S., called substance P, is present in the intestine [76]. This is interesting in view of the fact that after the administration of histamine liberators in animals hæmorrhages have been noted in the upper intestine. And in the literature [21] there is a report of a patient undergoing I.V. urography who died as a result of bronchospasm; at post-mortem there was blood in the upper intestine and an unexplained hæmorrhagic condition of the mucosa of stomach and duodenum.

REFERENCES

1 **Alyea E P & Haines C E** (1947) *J. Amer. med. Ass.* **135**, 25
2 **Amundsen A K** *et al.* (1956) *Acta radiol., Stockh.* **45**, 452
3 **Barry C N & Rose D K** (1953) *J. Urol.* **69**, 849
4 **Bassett R C** *et al.* (1953) *J. Neurosurg.* **10**, 38
5 **Batsakis J G** (1957) *Univ. Mich. med. Bull.* **23**, 45
6 **Baxter J D & Rose B** (1953) *J. Allergy* **24**, 18
7 **Bergman H & Ellner H** (1958) *Ann. intern. Med.* **48**, 105
8 **Bestermann E M M** *et al.* (1956) *Brit. med. J.* ii, 695
9 **Bhattacharya B K & Lewis G P** (1956) *Brit. J. Pharmacol.* **11**, 202
10 **Bloor B M, Wren F R & Hayes G J** (1951) *J. Neurosurg.* **8**, 435
11 **Bloor B M, Wren F R & Margolis G** (1951) *J. Neurosurg.* **8**, 585
12 **Bodman R I** (1951) *Proc. R. Soc. Med.* **44**, 635
13 **Bodner H, Howard A H & Kaplan H J** (1955) *J. Urol.* **74**, 422
14 **Broman T** *et al.* (1950) *Acta radiol., Stockh.* **34**, 135
15 **Broman T & Olssen O** (1948) *Acta radiol., Stockh.* **30**, 326
16 **Broman T & Olssen O** (1949) *Acta radiol., Stockh.* **31**, 321
17 **Broman T & Olssen O** (1956) *Acta radiol., Stockh.* **46**, 346
18 **Byrne J E & Melick W F** (1953) *Missouri Med.* **50**, 599

19 Celis A *et al.* (1956) *Acta radiol., Stockh.* **45**, 341
20 Cotrim E S (1954) *Acta radiol., Stockh.* Suppl. 16, 58
21 Crane J J (1939) *J. Urol.* **42**, 745
22 Crepea S B *et al.* (1949) *N. Y. St. J. Med.* **49**, 2556
23 Curry J J (1946) *J. clin. Invest.* **25**, 785
24 Curry J J (1946) *J. clin. Invest.* **25**, 792
25 Curry J J (1947) *J. clin. Invest.* **26**, 430
26 Dolan L P (1940) *J. Amer. med. Ass.* **114**, 138
27 Dotter C T & Jackson F S (1950) *Radiology* **54**, 527 (Cases 5 & 20)
28 Dotter C T *et al.* (1953) *Radiology* **60**, 691
29 Feldberg W (1956) In: Ciba Foundation Symposium on Histamine. Ed. G E W Wolstenholme & C O'Connor. London; p 4
30 Feldberg W & Paton W D M (1950) *J. Physiol.* **111**, 19P
31 Finby N, Poker N & Evans J A (1956) *Radiology* **67**, 244
32 Foeltz E L *et al.* (1952) *J. Neurosurg.* **9**, 68
33 Gilg E (1953) *Acta radiol., Stockh.* **39**, 299
34 Gordon A J *et al.* (1950) *Amer. J. Roentgenol.* **64**, 819
35 Green B & Sowerbutts J G (1956) *Brit. J. Radiol.* **29**, 161
36 Halpern B N (1956) In: Ciba Foundation Symposium on Histamine. Ed. G E W Wolstenholme & C O'Connor. London; p 92
37 Heathcote R St A & Gardner R A (1933) *Brit. J. Radiol.* **6**, 304
38 Herschfus J A *et al.* (1950) *Bull. New Engl. med. Cent.* **12**, 139
39 Herxheimer H (1953) *J. Physiol.* **122**, 49P
40 Howarth S (1950) *Brit. med. J.* ii, 1090
41 Idbohrn H (1956) *Acta radiol., Stockh.* **45**, 141
42 Idbohrn H & Berg N (1954) *Acta radiol., Stockh.*, **42**, 121
43 Koonce D H *et al.* (1952) *Amer. Heart J.* **44**, 901
44 Kraus H (1935) *Arch. exp. Path. Pharmak.* **179**, 537
45 Lecomte J (1952) *Arch. int. Pharmacodyn.* **92**, 241
46 Lecomte J (1955) *Arch. int. Pharmacodyn.* **101**, 375
47 Levitan A & Kroop G I (1959) *Amer. J. Roentgenol.* **82**, 779
48 Lourie E M (1942) *Ann. trop. Med. Parasit.* **36**, 113
49 Lourie E M & Yorke W (1939) *Ann. trop. Med. Parasit.* **33**, 289
50 Lowman R M *et al.* (1955) *Surg. Gynec. Obstet.* **101**,1
51 McAfee J G (1955) *Amer. J. med. Sci.* **229**, 549
52 McAfee J G (1957) *Radiology* **68**, 825
53 MacIntosh F C & Paton W D M (1949) *J. Physiol.* **109**, 190
54 Margolis G *et al.* (1956) *J. Neurosurg.* **13**, 349
55 Meszaros W T *et al.* (1959) *Dis. Chest* **36**, 642
56 Moll H H (1940) *Quart. J. Med.* **9**, 229
57 Mongar J L (1956) In: Ciba Foundation Symposium on Histamine. Ed. G E W Wolstenholme & C O'Connor. London; p 74
58 Mongar J L & Schild H O (1952) *J. Physiol.* **118**, 461
59 Morgan R H (1950) *Amer. J. Roentgenol.* **64**, 189
60 Mullen W H & Hughes C R (1952) *Amer. J. Roentgenol.* **68**, 903
61 Naterman H L & Robins S A (1942) *J. Amer. med. Ass.* **119**, 491
62 Nesbit R M & Lapides J (1950) *J. Urol.* **63**, 1109
63 Nesbit R M & Morrow J W (1959) *Amer. J. Roentgenol.* **82**, 849
64 Nesbit R M & Nesbitt T E (1953) *J. Urol.* **70**, 332
65 Nicolai C H (1956) *J. Urol.* **75**, 758
66 Nicolai C H *et al.* (1957) *Amer. J. Roentgenol.* **78**, 1061
67 Nosworthy M D (1948) *Anæsthesia* **3**, 86
68 Olssen O (1951) *Acta radiol., Stockh.* **35**, 65
69 Page J E *et al.* (1948) *Quart. J. Pharm.* **21**, 283
70 Paton W D M (1951) *Brit. J. Pharmacol.* **6**, 499
71 Paton W D M (1957) *Pharmacol. Rev.* **9**, 269
72 Payne W W, Morse W H & Raines S L (1956) *J. Urol.* **76**, 661
73 Pendergrass E P *et al.* (1942) *Amer. J. Roentgenol.* **48**, 741 (Case 4)
74 Pendergrass E P *et al.* (1955) *Amer. J. Roentgenol.* **74**, 262 (Cases 11 & 13)
75 Pendergrass P H *et al.* (1958) *Radiology* **71**, 1 (Case 52)
76 Pernow B (1955) In: Polypeptides which Stimulate Plain Muscle. Ed. J H Gaddum. London; p 25
77 Read R C (1959) *J. thorac. Surg.* **38**, 687
78 Riley J F & West G B (1955) *J. Path. Bact.* **69**, 269
79 Riley J F & West G B (1955) *Arch. int. Pharmacodyn.* **102**, 304
80 Robb G P & Steinberg I (1939) *Amer. J. Roentgenol.* **41**, 1
81 Robbins L E *et al.* (1951) *Radiology* **56**, 684
82 Robins S A (1942) *Amer. J. Roentgenol.* **48**, 766
83 Robinson A S (1956) *Arch. Surg., Chicago* **72**, 290
84 Rollins M *et al.* (1955) *Amer. J. Roentgenol.* **73**, 771
85 Root J C & Strittmatter W C (1959) *Amer. J. Roentgenol.* **73**, 769
86 Rose B (1951) *Annu. Rev. Med.* **2**, 155
(1952) *Recent Progr. Hormone Res.* **7**, 375
87 Rowe G W *et al.* (1956) *Circulation* **13**, 896
88 Rowley D A & Benditt E P (1956) *J. exp. Med.* **103**, 399
89 Runström G & Sigroth K (1950) *Acta med. scand.* Suppl. **246**, 176
90 Saltz N J *et al.* (1956) *Ann. Surg.* **144**, 118
91 Schild H O *et al.* (1951) *Lancet* ii, 376
92 Shaw R S (1956) *Surgery* **39**, 385
93 Simon S W *et al.* (1954) *J. Allergy* **25**, 395
94 Singer A G (1948) *Amer. J. Roentgenol.* **59**, 727
95 Sisson J H *et al.* (1945) *Johns Hopk. Hosp. Bull.* **76**, 93
96 Sloan R D & Cooley R N (1953) *Radiology* **61**, 701
97 Steinberg I *et al.* (1959) *Amer. J. Roentgenol.* **82**, 758
98 Taussig H B & Bing A J (1949) *Amer. Heart J.* **37**, 555
99 Taylor H K & McGovern T (1943) *J. Amer. med. Ass.* **121**, 1270
100 Utterback R A & Haymaker N (1952) *J. nerv. ment. Dis.* **116**, 739
101 Wall B & Rose D K (1951) *J. Urol.* **66**, 305
102 Weatherall M (1942) *Brit. J. Radiol.* **15**, 129
103 Weiss S *et al.* (1929) *Amer. Heart J.* **4**, 664
104 Weiss S *et al.* (1932) *Arch. intern. Med.* **49**, 360
105 Whiteleather J E & De Saussure R L (1956) *Radiology* **67**, 537
106 Winter C C (1955) *J. Urol.* **74**, 416
107 Zeitel B E (1956) *J. Urol.* **76**, 461

Dr J N Pattinson (*London*)
Radiological Aspects

Angiocardiography was introduced during 1937 and 1938 as a method for the investigation of congenital heart disease. It can also be very useful in the examination of many abnormalities found in the thorax, not only those affecting the heart, but also in lesions of the mediastinum and lungs. But congenital heart disease is the most frequent indication for angiocardiography, and this group of abnormalities is the most exacting from the technical aspect. During the last decade angiocardiographic techniques have greatly improved, in parallel with, and stimulated by, the great advances in cardiac surgery and clinical diagnosis.

Angiocardiography carries the risk of a severe or fatal reaction and the mortality is greatest in congenital heart disease. This mortality is high for a diagnostic procedure. Patients should therefore be carefully selected, with full consideration given to the value of the information likely to be obtained, and the best available equipment must be used.

Angiocardiography can be useful in making a diagnosis and in providing anatomical information. In the early days a diagnosis was usually sufficient. Now, a correct diagnosis is made in most cases on the clinical examination, aided by cardiac catheterization and dye dilution studies. It is anatomical information which is most often required, to assist the surgeon in deciding on operability, in selecting the most suitable operative technique and in choosing the appropriate type of anæsthesia.

The technical requirements for the production of a satisfactory angiocardiogram are as follows:
(1) *Rapid serial films:* The size and shape of the cardiac chambers and of stenotic segments change greatly during the cardiac cycle. The full range of these variations must be demonstrated if the anatomy is to be accurately assessed. A minimum of 6 to 8 films per second is therefore required in adults and children, and in infants 10 to 12 films

per second are needed. When films are taken at slower speeds, small intracardiac shunts may be missed and it may be impossible to determine the exact site of even a large shunt.

(2) *Simultaneous exposure of films in two planes at right angles to one another:* The chambers of the heart and the great vessels overlap one another to some extent in any one plane. Not infrequently, intracardiac shunts and stenotic segments may be difficult or impossible to detect in one view, or their exact size and site may be in doubt. With simultaneous bi-plane films, the configuration of the cardiac chambers, &c., is demonstrated in two dimensions. Therefore their anatomy can be evaluated precisely and errors in interpretation are reduced to a minimum. The same information cannot be obtained by taking a second angiocardiogram in a different position with a single-plane film changer. There is also an increased risk of a fatal reaction when multiple injections are given shortly following one another.

(3) *A powerful generator* is required to allow the use of very short exposure times. Exposures of 3 to 10 msec are required to demonstrate the normal valve cusps. With longer exposures, these structures are often rendered invisible due to movement blur. A stenosed valve is much easier to show since it remains fixed in position throughout most of the systolic phase.

(4) *Selective injection of the contrast medium:* For many years, the contrast medium was always injected into a peripheral vein, either percutaneously or through a cannula. This is still the simplest, quickest and safest way of obtaining an angiocardiogram. Unfortunately it is unsatisfactory in congenital heart disease and is useless for the investigation of many types of abnormality.

In the selective method, the contrast medium is injected directly into a cardiac chamber or into one of the great vessels immediately proximal to the site of the lesion. The injection is made through a cardiac catheter, or through a long polythene tube or needle inserted percutaneously. Some form of pressure injector is essential, for the contrast medium must be delivered rapidly. This technique allows the contrast medium to be injected undiluted at the important site, and this area is not obscured by structures proximal to it since the latter are not opacified. Even more important, the contrast medium can be injected proximal to any shunt, even a left-to-right shunt. Thus a defect can be clearly shown which is impossible to demonstrate by a peripheral intravenous injection.

Insertion of the cardiac catheter, &c., demands careful fluoroscopic control and in addition pressure recordings are often required to ensure correct positioning of the catheter tip. An image intensifier is a great advantage during catheterization. It is then easier to see the catheter and the normal room illumination can be maintained during fluoroscopy. This helps the anæsthetist; it reduces the time of the examination, since dark adaptation is unnecessary and pressure recordings, &c., can be carried out more rapidly. The amount of radiation received by the patient and personnel is also reduced.

It is therefore obvious that the single-plane film changer providing 1 to 2 films per second is worse than useless in the investigation of congenital heart disease. The patient is exposed to the full risk of an angiocardiogram, but the anatomical information obtained will be inadequate and an important peripheral vein will have been destroyed.

Cardiac catheterization and angiocardiography are complementary methods in the investigation of congenital heart disease. In some cases either catheterization or angiocardiography will provide all the necessary information; in others both are needed. Ideally, cardiac catheterization is done first and the results evaluated. The findings will indicate where the selective injection should be made. The catheter tip is then carefully positioned under fluoroscopic and manometric control. The fluoroscopic table should have a sliding top so that the patient can be moved over the film changer without any risk of dislodging the catheter. There are many advantages in combining angiocardiography with cardiac catheterization. Only one anæsthetic is needed and the discomfort to the patient is reduced. The amount of radiation is decreased, the minimum number of peripheral veins are used and much time is saved.

With the advent of open cardiotomy it became possible for the surgeon to assess the internal anatomy on the operating table. But the value of angiocardiography has not diminished, it has increased. The choice of surgical technique and type of anæsthesia varies with different lesions and it is therefore all-important to demonstrate the anatomy before operation.

Dr R W Emanuel (*London*)
Observations on Mortality

The mortality of angiocardiography varies from 0·2 to 4·0% (Lester 1961). A risk of this order is extremely high for any investigation and compares most unfavourably with the mortality of cardiac catheterization which, in similar cases, is between 1 and 2 per 1,000 (Wood 1956). Nevertheless, angiocardiography is frequently necessary, and now has an established place in the investigation of cardiac cases.

In 472 patients investigated at the Middlesex Hospital, there were 7 deaths, a mortality of 1·5%.

These cases have been analysed to determine whether there was any clinical or pathological factor which increased the risk of angiocardiography.

The anatomical diagnosis in the 7 fatalities and the presence of cyanosis and pulmonary hypertension is shown in Table 2 of Dr Lester's paper (p. 470). Cyanosis at one time was thought to increase the risks of angiocardiography, but this was not so in the present series. The mortality in the cyanotic cases investigated was 1·4%. This was slightly less than the risk in the acyanotic cases in which the mortality was 1·5%.

A more important factor appeared to be pulmonary hypertension which, although present in only 26 of the 472 patients investigated, occurred in 4 of the fatalities, a mortality of 15·4% (Table 1). This is in sharp contrast with the 61 patients who had similar anatomical lesions (left-to-right shunts 57 cases: mitral valve disease 4 cases), which were not complicated by pulmonary hypertension. There was no death following angiocardiography in this group. The remaining two groups were selected as additional controls (Table 1). Sixty-eight patients with aortic and left-sided lesions (aortic valve disease 24 cases: aneurysm of aorta 23 cases: coarctation of aorta 20 cases: systemic hypertension 1 case) were investigated by venous angiocardiography with one fatality, which occurred in the patient with systemic hypertension, a mortality of 1·5%. The final group of 72 patients with normal hearts and normal systemic and pulmonary pressures were investigated without mortality. It appears therefore that pulmonary hypertension greatly increases the risk of angiocardiography.

Table 1
The effect of pulmonary hypertension on the mortality in angiocardiography

Cases	*No.*	*Deaths*	*Mortality rate %*
Pulmonary hypertensive	26	4	15·4
Similar cases without pulmonary hypertension	61	0	0
Aortic lesions	68	1	1·5
Non-cardiac	72	0	0

Pulmonary stenosis was the other factor which, under certain circumstances, influenced the mortality. The 472 patients investigated included 185 with pulmonary stenosis (Table 2). Fallot's tetralogy accounted for 147 of these and there was no death in this group following angiocardiography. In the 38 patients with pulmonary stenosis and normal aortic root, however, there were 2 deaths, a mortality of 5·3%. The main anatomical difference between these two groups is that cases of Fallot's tetralogy have a ventricular septal defect which can act as a safety valve, allowing a right-to-left shunt to occur whenever the right ventricular pressure exceeds systemic level. This mechanism is denied cases of pulmonary stenosis with normal aortic root.

Table 2
The effect of pulmonary stenosis on the mortality in angiocardiography

	No.	*Deaths*	*Mortality rate %*
Fallot's tetralogy	147	0	0
Pulmonary stenosis, with normal aortic root	38	2	5·3

In 6 of the 7 fatalities there was severe right ventricular hypertension and in 4 of these there was no ventricular septal defect. This suggests that in cases where the right ventricular outflow is obstructed by such lesions as pulmonary hypertension or pulmonary stenosis without a ventricular septal defect, the risk of angiocardiography is increased.

REFERENCES
Lester E R (1961) *Proc. R. Soc. Med.* 54, 469
Wood P H
(1956) Diseases of the Heart and Circulation. 2nd ed. London

Dr W Somerville (*London*)
The angiotoxic effect of contrast medium mentioned by Dr Mann is illustrated by the occasional development of localized pulmonary œdema after injection through a cardiac catheter to demonstrate a segment of the pulmonary vasculature. The hazard of angiocardiography in severe pulmonary stenosis may be related to the hold-up of the contrast medium in the pulmonary vessels in this condition, rather than to any sudden increase in right ventricular pressure resulting from selective injection into that chamber.

Dr A J H Hewer (*London*)
Sarnoff & Sarnoff (1952) published an account of their investigations into the production of acute pulmonary œdema by an intracisternal injection of fibrin. The disturbance was shown to be produced by a widespread peripheral vasoconstriction which squeezed blood into the less vasotonic pulmonary circulation with a consequent rise in pulmonary arterial and venous pressure, producing a sudden right-sided heart failure. It has been shown that in some of the cases mentioned, where there was a reaction to the injection of contrast medium, there was an intracerebral change of an anaphylactoid nature. If this is so, it might reflexly produce a pulmonary hypertension and heart failure and might, therefore, be prevented by an intravenous infusion of 30% urea solution.

REFERENCE
Sarnoff S J & Sarnoff L C (1952) *Circulation* 7, 54

Section of Dermatology

President Hugh Gordon MC FRCP

Meeting February 16 1961

Symposium on Malignant Melanoma

Histopathology of Cellular Nævi and Malignant Melanomas

by Henry Haber MD (*London*)

The term nævus designates a circumscribed local malformation of tissue structures which may be present at birth or appear later in life. A cellular nævus is characterized by the presence of nævus cells.

The clear cell: Clear cells are highly specialized round cells, with clear cytoplasm and small dark nuclei which are seen singly at fairly regular intervals between the basal cells. Special silver staining methods show that they have a number of fine dendritic processes. The function of the clear cells is to produce melanin which protects the skin from excessive irradiation by the sun. Bloch has demonstrated a ferment within the clear cells capable of converting dopa (3–4 dihydroxyphenylalanin) into melanin. It has been suggested that the clear cells (also known as melanocytes) inject their pigment, by means of their dendrites, into the neighbouring basal cells, where the pigment appears in the form of dark caps covering the nucleus (Masson 1948).

The skin is a large sensory organ and is, therefore, supplied with a vast nerve apparatus to mediate sensations of heat, cold, touch and pain. Special nerve endings are seen in the skin: (1) Free nerve endings terminating within the epidermis, (2) encapsulated nerve endings lying in the dermis, the best known being the Wagner-Meissner corpuscles and Vater-Paccini bodies of the deeper structures of the cutis, and (3) the nerve ends surrounding hair shafts (Winkelmann 1960).

There are two schools of thought regarding the histogenesis of cellular nævi. The older school, led by Unna and Allen, suggests that the clear cells are modified epidermal cells, which by simple multiplication produce all types of cellular nævi. All nævi are, therefore, of ectodermal origin. The second school, led by Masson, believes that cellular nævi derive their origin either from clear cells or the Schwannian cells of the neural tree of the skin, or from both sources. The clear cells are not modified epidermal cells but neural elements immigrating into the epidermis from the neural crest. As the neural tree is also of the same origin, all cellular nævi are neuro-ectodermal structures (Allen 1949, Masson 1951).

Lentigo (Fig 1): This is a light or dark brown macule appearing on any part of the body. It may be present at birth or appear at any age. It shows histologically a circumscribed acanthosis with hyperpigmentation of the basal cell layer. The lesion may disappear or persist for life and has to be regarded as a simple type of pigmented nævus.

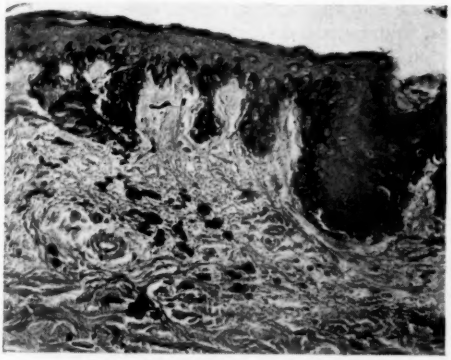


Fig 1 *Lentigo. The epidermis shows acanthosis. The basal cell layer exhibits hyperpigmentation and the presence of many clear cells. The pigment is being shed via the normal process of keratinization and appears in coarse granules within the stratum corneum. Part of the pigment is also dropped into the corium where it is being picked up by chromatophores*

Junctional nævus (Fig 2): The lesion is a hairless brown macule which cannot be distinguished clinically from a lentigo. It is present at birth or

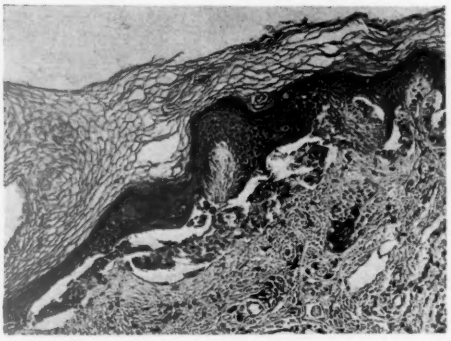


Fig 2 *Junctional nævus. At the epidermo-dermal junction there are many clear cells segregated from the rest of the epidermis by a clear space. The upper corium shows chromatophores heavily laden with melanin, provoking a lymphocytic round cell infiltration. There is absence of an invasion of the epidermis by the clear cells*

may appear after. In any case it is a lesion of the younger age group. It is to be found on the lower extremities, soles, palms and genitalia, but also on any part of the body.

The microscope reveals clusters of clear cells segregated from the rest of the epidermis at the epidermo-dermal junction. Hence the name junctional nævus. The cells have a clear cytoplasm and darkly staining nuclei and varying amounts of melanin. Mitotic figures are not seen.

Compound nævus (Fig 3): A junctional nævus may enlarge by multiplication of the clear cells which migrate into the dermis. Nævus cells are, therefore, found at the epidermo-dermal junction and within the dermis. Hence the term compound nævus.

Intradermal nævus (*common mole*) (Fig 4): After a time junctional activity may stop when no more nævus cells are segregated. All the nævus cells lie now within the dermis and at this stage the epidermis attains a normal appearance again. An intradermal nævus has formed. The nævus cells lie within the dermis arranged in characteristic alveoli or ribbons; they have lost the typical features of clear cells and appear more or less as round, dark nuclei of the size of a lymphocyte. Some of the cells have a thin rim of eosinophilic cytoplasm, which may contain vacuoles. On the whole the cells are recognizable by their arrangement to each other, rather than by their morphology.

Some nævus cells coalesce to form characteristic giant cells. It should be pointed out, however, that some nævi may also be formed by a combination of segregating clear cells and the Schwannian cells of the neural tree. Some may be pure 'Schwannomas'. This is clearly seen in nævi containing neurofibroma-like tissue, arranged in

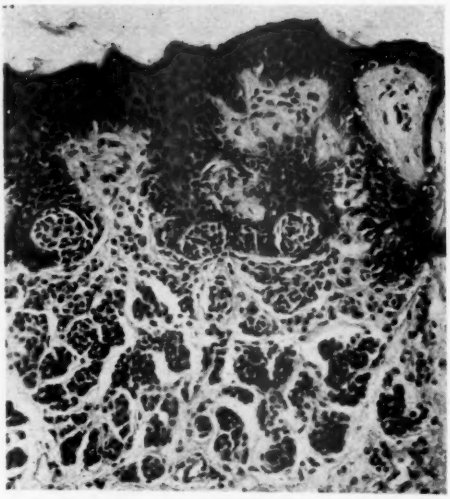


Fig 3 *Compound nævus. The epidermis exhibits marked acanthosis and segregation of nævus cells at the tips of the rete pegs. Within the upper corium nævus cells in typical nests are seen. The round cell infiltration is mild*

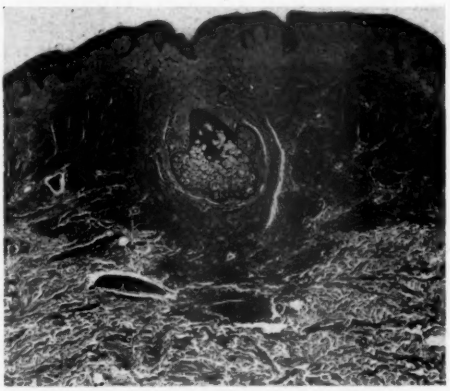


Fig 4 *Intradermal nævus. Clinically it represents a common mole. The epidermis looks normal. Separated by a band of normal connective tissue there are dense infiltrations of nævus cells in typical arrangement. Inflammatory reaction does not usually occur*

concentric lamellæ in which nævus cells are present. These structures are known as 'lames foliacées' and neural tubes respectively. The 'lames foliacées' simulate Wagner-Meissner corpuscles. This type of mole is seen in the older age group.

Intradermal nævi may sometimes enlarge, become irritable, and painful. Histological examination in such cases will reveal follicular abscesses due to infection or trauma, following mechanical

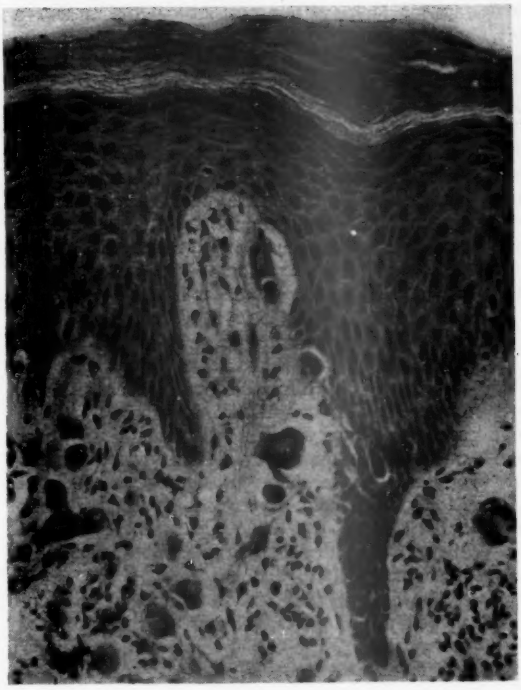


Fig 5 *Juvenile melanoma. Note the segregation of bizarre-looking multinucleate giant cells*

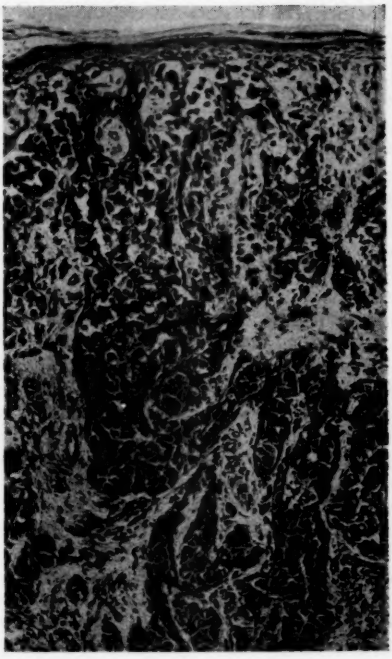


Fig 7 *Malignant melanoma. Note the characteristic segregation of malignant nævus cells invading both the epidermis and cutis*

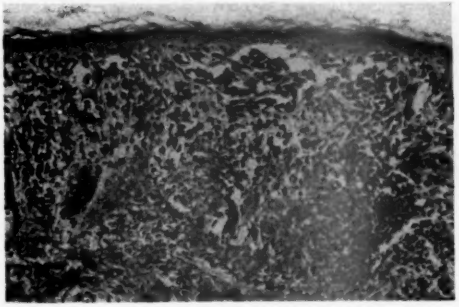


Fig 6 *Malignant lentigo. The epidermis is atrophic and there is marked junctional activity along the epidermo-dermal junction with inflammatory reaction in the upper cutis*

epilation of hairs in the moles. Sometimes foreign-body granulomas due to disintegrating follicles are observed. In some cases degenerated follicles undergo calcification with bony metaplasia.

Juvenile melanoma (Fig 5): Juvenile melanoma is a peculiar type of cellular nævus occurring before puberty (Spitz 1951, Haber 1952). Clinically, the lesion may be single or multiple, appearing on the face, extremities or any part of the body. It may simulate an initial lesion of lupus vulgaris by its red colour, or may be mistaken for a verruca or even a malignant melanoma when it is verrucous or bleeds after trauma. The characteristic histological appearance consists of epidermal hyperplasia and segregation of epithelioid-looking nævus cells with bizarre giant cells containing vacuoles. Œdema in the upper parts of the corium, dilated vessels, inflammatory changes, mitotic figures complete the picture. The lesion suggests a malignant melanoma, but the clinical course is benign. The lesion occurs in adults as well but its position is debatable.

Malignant lentigo (Fig 6): The lesion occurs in older patients. It is mostly seen on the face or exposed parts of the body as a slowly spreading, slightly raised, more or less heavily pigmented lesion of irregular outline. The lesion may spread for ten to twenty years or more and may occupy considerable areas of the skin. It may persist as such for ever, or may become nodular when true malignancy commences.

The histological picture shows segregation of clear cells at the epidermo-dermal junction, with invasion of the epidermis and disintegration of its

structure. The cells are bizarre, the nuclei hyperchromatic and pigmentary activity is considerable. The upper cutis shows numerous pigmented cells, partly nævus cells and partly chromatophores, arranged in a haphazard manner and surrounded by a considerable inflammatory reaction. After many years the lesion, which has been spreading along the epidermo-dermal junction, may change into an invasive tumour when it becomes a malignant melanoma. Malignant lentigo is to be regarded as a pre-invasive melanoma in the same way as Bowen's intra-epidermal carcinoma may precede a frank squamous cell epithelioma (Dubreuilh 1912).

Malignant melanoma (Fig 7): The majority of cellular nævi arise by benign multiplication of clear cells; malignant melanomas develop by malignant transformation of the same cells. These are fundamental facts. Melanomas are, therefore, seen to arise in normal skin, in junctional nævi, compound nævi and malignant lentigines. Common moles are notoriously benign and do not transform into malignant melanomas. Some slightly pigmented or non-pigmented junctional or compound nævi may be clinically invisible, a fact which may explain the occurrence of malignant melanomas in 'normal' skin. On the other hand, there is no reason to doubt that a malignant melanoma may rise *ab ovo* from normal clear cells by malignant transformation.

Malignant melanoma is one of the most unpredictable and most dangerous of malignant tumours, spreading via lymphatics and blood vessels to any organ of the body. If a pigmented nævus enlarges, irritates, becomes darker and bleeds, then the chances are that it has become malignant. Lesions exposed to continuous friction in intertriginous areas should be removed before they give cause for trouble. There is absolutely no danger in removing pigmented lesions prophylactically. Biopsies of pigmented lesions are deplorable and should never be carried out, as even a clinically benign-looking lesion may have undergone malignant transformation which can only be detected microscopically.

The histological diagnosis of a commencing melanoma in a nævus is one of the most difficult problems in histopathology and largely depends on the individual experience and knowledge of the examiner. Increased junctional activity, hyperpigmentation of cells, invasion of the upper strata of the epidermis, mitotic figures and a marked inflammatory reaction in the upper cutis, are the outstanding criteria of a commencing malignancy.

The invading cells of a malignant melanoma vary in their morphology. They may be round, oval, or spindle-shaped. They may be arranged in alveoli or fascicles or they may form medullary structures. The cells as seen in cytological smears appear large with abundant cytoplasm and a round, dark nucleus. Many cells are multinucleated. Mitotic figures may be abundant or scanty. Melanin in the form of coarse granules or dust may occupy either the whole cell or the nucleus only. Some lesions have a surprisingly uniform cytology and melanin may be completely absent. The so-called amelanotic melanomas may be very difficult to diagnose. The outstanding feature is the presence of junctional activity. Melanomas are usually solitary lesions, but melanomas arising in several nævi simultaneously or subsequently, are not uncommon (Miescher 1933).

The Mongolian spot (Fig 8): This condition occurs in the Mongolian race as a palm-sized slaty blue macule, occupying the sacral or gluteal region. It is present at birth and disappears about puberty or may persist into adult life. Aberrant Mongolian spots may occur in other races when they appear on the shoulder and trunk. Nævus fusco-ceruleus ophthalmico-maxillaris of Ota is an aberrant Mongolian spot occupying the skin of the cheek and eyelids (Cole *et al.* 1950, Parisier & Beerman 1949). It also invades the orbit and the eye, leading to melanosis.

The histological picture shows scattered ribbon-shaped melanoblasts, lying in the spaces of the collagen.

Fig 8 *Mongolian spot. Characteristic ribbon-shaped Mongolian cells in the cutis*

Blue nævus (Fig 9): The blue nævus is the 'pathological' counterpart of the Mongolian spot. It occurs in all races as a solitary bluish nodule embedded in the skin of the face, dorsa of hands and feet. It has not been observed in the skin of palms and soles. The lesion consists of masses of ribbon-shaped melanoblasts and chromatophores, heavily laden with melanin granules (Montgomery & Kahler 1939).

The blue nævus of the cellular type contains besides melanoblasts and chromatophores also cells of the Schwannian type, arranged in fascicles.

Mongolian spots do not undergo malignant change. Ota's nævus is known to have undergone

Fig 9 *Blue nævus. Masses of characteristic ribbon-shaped cells heavily laden with melanin*

malignancy in a few instances. Blue nævi rarely become malignant (Herzberg & Klein 1961).

The ribbon-shaped Mongolian cell is seen to accompany nerves in amphibians and low vertebrates. It is also seen in the skin of apes. It is, therefore, possible to regard Mongolian spots and blue nævi as atavistic relics.

REFERENCES
Allen A C (1949) *Cancer* **2**, 28
Cole H N jr, Hubler W R & Lund H Z (1950) *Arch. Derm., Chicago*, **61**, 244
Dubreuilh W (1912) *Ann. Derm. Syph., Paris* 3, 129
Haber H (1952) *Trans. St John's Hosp. derm. Soc., Lond.* **31**, 44
Herzberg J J & Klein U E (1961) *Arch. klin. exp. Derm.* **212**, 158
Masson P (1948) In: The Biology of Melanomas. Ed. M Gordon *et al.* New York; p 15
(1951) *Cancer* **4**, 9
Miescher G (1933) In: Jadassohn's Handbuch der Haut- und Geschlechts-Krankheiten. Berlin; XII/3, 1007
Montgomery H & Kahler J E (1939) *Amer. J. Cancer* **36**, 527
Parisier H & Beerman H (1949) *Arch. Derm., Chicago* **59**, 396
Spitz S (1951) *Amer. J. Path.* **24**, 591
Winkelmann R K (1960) Nerve Endings in Normal and Pathologic Skin. Springfield, Ill.

Malignant Melanoma in Pregnancy [*Summary*]

by Phyllis A George FRCS (*London*)

Miss George showed that, contrary to general belief, pregnancy did not worsen the prognosis of malignant melanoma. She said that 115 patients in whom pregnancy and melanoma coincided were compared with 330 controls. The clinical course in both groups was essentially the same except that there were more instances of lymph-node metastases in the study (i.e. pregnant) group at the time of definitive treatment. There was, however, no evidence of any increased rapidity of spread as would be suggested by a higher incidence of generalized metastases or immediate regional spread. Five- and ten-year survival rates of 47% and 42% respectively were found for the group as a whole. An interesting feature of this study was the apparently good prognosis for female patients in general.

(A full account of this work has appeared in *Cancer*, 1960, **13**, 854.)

The Treatment of Malignant Melanoma by Perfusion Techniques

by Professor W T Irvine MD ChM FRCS and C F Noon MA FRCS (*London*)

Attempts to destroy malignant cells by chemotherapeutic methods have been in use for nearly twenty years (Rhoads 1946, Goodman *et al.* 1946, Wilkinson & Fletcher 1947). The alkylating agents were the drugs most commonly used. Their administration systemically, however, had serious limitations. The dose required to destroy malignant cells frequently produced toxic effects on normal tissues, the hæmopoietic system and the gastrointestinal tract being the most sensitive to damage.

In order to overcome these difficulties and permit a higher concentration of the drug, Creech *et al.* (1958) introduced techniques whereby the tumour-bearing area of the body was isolated from the systemic circulation and its blood supply maintained by means of a pump oxygenating machine. By reducing the amount of the agent reaching the marrow and gastrointestinal tract, much higher levels could be administered to the tumour-bearing area. These authors later extended their technique to include patients with widespread malignant disease, carrying out total body perfusion after removal of some of the patient's own marrow for re-infusion later when the drug was thought to be inactive.

Clinical cases: The melanomas treated and the types of perfusion are shown in Tables 1 and 2. The cytotoxic agent used for the treatment of malignant melanoma has been phenylalanine mustard (melphalan) in all cases.

Dosage and mode of administration: The dosage of cytotoxic agents tolerated by regional perfusion has not yet been definitely stabilized. These techniques reduce damage to the hæmopoietic system and gastrointestinal tract, enabling larger amounts to be given. When measurements at the time of perfusion demonstrate minimal leakage into the general circulation, damage to the normal tissues in the perfused region is the limiting factor controlling dosage.

Table 1
Malignant melanoma
12 isolated perfusions

	Lower limb	*Upper limb*	*Pelvic*
Primary treatment	4 cases		
Prophylactic following surgery and no recurrence	3 cases		1 case
Previous surgery now with recurrence	2 cases	1 case	1 case

Table 2
Cases treated by whole body perfusion

Type of tumour	*Drug used*	*Result*
Large primary melanoma of neck with melanomatosis	Melphalan 120 mg	Destruction of primary tumour
Melanoma of right leg with pelvic secondaries	Melphalan 120 mg	Peripheral necrosis of many secondary deposits
Melanomatosis	Melphalan 140 mg	Died at 12 days
Melanomatosis with cerebral secondaries	Melphalan 120 mg	Died at 4 weeks
Melanomatosis	Melphalan 120 mg	Died at 2 weeks
Melanomatosis	Melphalan 140 mg	Marked regression

Extracorporeal circuit and technique: The artery and vein supplying the tumour-bearing area are isolated and polythene cannulæ are inserted.

The extracorporeal circuit consists of an Ormond Mono pump delivering the venous outflow through a disposable plastic bubble oxygenator. From there the oxygenated blood is pumped by a second Mono pump through a heat exchange mechanism to the arterial cannula. Perfusion pressures are monitored and kept 10 mm Hg below the patient's systemic arterial pressure. Flow rates are adjusted to achieve the desired pressures. The leak between the two systems is measured with ^{51}Cr-labelled red cells. The perfusion is continued for about one hour.

In total body perfusions the drug is usually simply administered through an arterial cannula inserted in such a manner that it can be infused into the region of the body most involved. Immediately prior to the injection, marrow is aspirated from the sternum and iliac crests and stored with heparin and 119 Glaxo tissue culture medium at 4° C. It is replaced the following day by intravenous injection.

Results

Many of the patients with malignant melanoma treated by perfusion with phenylalanine mustard have shown some evidence of regression.

The effects obtained in one patient treated are outlined in the following case report:

Case Report *Diffuse Melanomatosis*

L P, male, aged 57

History: For several years he had noticed a mole on the right side of his neck. This increased in size and in May 1958 it was excised and at the same time two other moles, one on his chest and one on his scalp, which had appeared earlier that year were excised. The pathological report was superficial melano-carcinoma.

Soon after this excision the melanoma on his neck recurred and others appeared all over his body. These gradually increased in size and new ones appeared continuously. Many of them were painful and the massive neck tumour produced severe brachial neuralgia.

On admission: In the right supraclavicular fossa there was a large fungating purplish mass about 6×4×4 cm, which was completely fixed posteriorly. Numerous subcutaneous and subcuticular nodules, some melanotic and some not, were situated all over his body. Glands were palpable in the left supraclavicular fossa, both axillæ and both groins.

Operation (27.1.60): Marrow was aspirated from the sternum and iliac crests before perfusion, which was carried out through the right femoral artery and vein with the tips of the cannulæ lying in the inferior vena cava and arch of the aorta. 120 mg of melphalan was given in two doses and the perfusion continued for two hours. The marrow was replaced the following day by intravenous injection.

Post-operative progress: At the end of the first post-operative week it was apparent that the lesion in his neck was changing. It had become smaller and more mobile. There was also a good deal of bleeding from its base. Many of the subcutaneous lesions became erythematous. His white blood cell count and platelet count dropped steadily until about the twelfth day when recovery commenced. About six weeks after the operation the large tumour on the right side of his neck had separated leaving a granulating base which was skin-grafted. Up to this stage his general condition had remained reasonably satisfactory. Unfortunately eight weeks after the operation his general condition deteriorated, he developed a septicæmia and died. Immediately prior to death his white cell count was 7,300 (polys. 76%). Autopsy revealed no obvious source of infection.

Comment: The effects of melphalan on melanomas are well illustrated in this patient. The smaller tumours rapidly become surrounded by an acute inflammatory reaction and may completely disappear. The larger tumours frequently become œdematous in the immediate post-operative period – many then shrink and since the more superficial parts of the tumour appear to undergo necrosis the tumour separates from the surrounding skin and frequently a fixed tumour will become mobile and the whole tumour become detached from its base. It is not always an advantage to await the tumour's separation since the necrotic mass may become infected and malodorous. Instead, if the tumours have been made necrotic they are easily enucleated digitally under anæsthesia, the melanomas shelling out from the

normal surrounding tissue like prostatic adenomata when the finger enters the space left by the peripheral necrosis.

Complications: The complications seen in these perfusions are outlined in Table 3. Marrow depression has been the most serious complication and has occurred in approximately half of the regional perfusion cases.

Of the local complications œdema and skin blistering are the most common and skin blistering must be considered evidence that the dose employed was too high.

Table 3
Complications

General		
	Shock	
	Marrow depression	
	Gastrointestinal disturbances	
	Liver damage	
Local		
	Œdema	
	Skin changes:	erythema
		blistering
	Vascular damage	
	Wound sepsis	

REFERENCES
Creech O, Krementz E T, Ryan R F & Winblad J N (1958) *Ann. Surg.* **148**, 616
Goodman L S, Wintrobe M M, Dameshak W, Goodman M J, Gilman A & McLennan M T (1946) *J. Amer. med. Ass.* **132**, 126
Rhoads C P (1946) *J. Amer. med. Ass.* **131**, 656
Wilkinson J F & Fletcher F (1947) *Lancet* ii, 540

The Radiosensitivity of the Malignant Melanoma [*Summary*]

by M Lederman FFR (*London*)

The treatment of the malignant melanoma is dominated by two traditional beliefs, the first of which is that these tumours are highly virulent and almost uniformly deadly, and the second that all of them are radioresistant. It is because of these beliefs that the radiotherapist has little opportunity of treating these tumours.

At the Royal Marsden Hospital I have seen some 200 pigmented tumours affecting the eye and its neighbourhood, the patients having been referred from Moorfields or the Royal Eye Hospital. Among them were some 70 malignant melanomas affecting the limbus, the conjunctiva and the lids, and from an experience gained in the treatment of these particular tumours three conclusions can be reached:

(1) That many of the malignant melanomas affecting the conjunctiva and lids are radiosensitive, and the radiosensitivity depends on the situation of the tumour in relation to the limbus; the nearer the limbus the greater the radiosensitivity; the more the lid and fornices are involved the less the radiosensitivity.

(2) The tumours are not highly malignant, having a very long history, and metastasis was observed in some 10% of the cases, almost all of which were recurrent after previous inadequate and repeated local treatment.

(3) A biopsy is not a dangerous procedure provided positive steps are taken in the event of a positive report.

[A series of slides was shown illustrating the satisfactory results that can be obtained by radiotherapy in the treatment of limbal and conjunctival melanomas, the eye being preserved in most cases.]

It would, of course, be unwise to apply the results of experience gained in the treatment of the epibulbar malignant melanoma to malignant melanomas arising from other skin and mucosal areas. There is no certainty that the pigmented tumours in this region are in fact comparable to those occurring in other parts of the body: it is more than possible that the different forms of malignant melanoma occurring in different parts of the body may have little in common apart from their pigment.

Nevertheless, the response to radiation would suggest that the sensitive tumours of the conjunctiva and limbus are probably of basal epithelial origin, whereas the insensitive ones often associated with a pre-existing nævus might well, as Masson suggests, be of neuro-ectodermal origin, in which event their radioresistance could be expected.

Without wishing to speculate too much, our experience would seem to justify a plea for the reassessment both of the place of radiotherapy and the treatment generally of the malignant melanomas.

There is no doubt that the results of treatment of malignant melanoma are at least as good as those obtained in the treatment of cancer of the breast or buccal cavity, and bearing this in mind there should be a less emotional approach to the treatment of this disease. Many of the decisions now taken, particularly those in connexion with the need for ultra-radical surgery, are based on fear and speculation rather than true knowledge. A more intensive and planned study of the natural history of the disease and a more balanced approach to its treatment problems may well show that there is a definite place for radiotherapy and that many of the very extensive and mutilating operations now being practised might perhaps be reduced in scope.

[A fuller account of this work has appeared in *Brit. J. Radiol.*, 1961, **34**, 21.]

Some Results of a Survey of Melanomas

by N Petersen FRCS, D C Bodenham FRCSEd and O C Lloyd MD

Mr D C Bodenham (*Bristol*) reports:

In 1947 we set out as a co-ordinated surgical team with Dr O C Lloyd, pathologist, to find out all we could about malignant melanomas.

During the fourteen years we have personally had under our care some 250 melanomas and had the opportunity of reviewing another 400 consecutive cases registered with the South Western Regional Cancer Bureau.

The incidence in the South West is at least 1·8 per 100,000 and the disease is twice as common in females as in males. It is significant that in this region the average survival for melanomas is 5% better than for all cases of carcinoma of the breast.

Melanoma of the leg is particularly common in females under 50 years and generally this area carries the best prognosis with 75% free of disease at five years. The foot, however, though much less frequently affected has only a 25% chance. The trunk also does badly and both these sites are associated with a high incidence of invaded lymph nodes when first seen.

We have found that two-thirds of the melanomas in our series have arisen in pre-existing benign lesions which are nearly always lentigines; over one-third were present at birth, and one-third had been present over ten years; only a few melanomas arose in pigmented nævi.

Ulceration at the time of first treatment is associated with a poor prognosis but those lesions which have not ulcerated have done well. Cell type does not affect prognosis but when invasion of the dermal lymphatics is seen microscopically dissemination is likely but not inevitable.

We have studied the results of prophylactic radical lymph-node dissection and found the results are better if an interval of three weeks elapses between excision of the primary and the node clearance. It is believed that the stasis which follows node clearance holds up migratory cells in the lymphatics where they are inaccessible to surgery and that if an interval is allowed they travel to the nodes where they are halted and removed at operation.

Simultaneous dissection in continuity is the method of choice where the primary and lymph nodes are in reasonable proximity.

The results of therapeutic node dissection are poor by comparison.

We have made a careful study of trauma and been unable to incriminate trauma as a causative factor in malignancy. We have, however, been impressed by the significant and adverse effect of trauma on the established lesion. Those subjected to deliberate trauma, i.e. incisional biopsy, curettage, diathermy, cauterization or application of CO_2 snow, have all done badly.

It appears that trauma not only tends to spread the disease but delays definitive treatment. Biopsy material taken by sampling has often led to errors of diagnosis since the material is not necessarily representative of the lesion as a whole.

We have found that clinical diagnosis by experienced observers based on a careful history and naked-eye examination is correct in 90% of cases and definitive treatment can then be carried out without delay; if there is doubt then an excision with a 1 cm margin is carried out and if positive a suitable radical excision follows.

Treatment should have one object – to rid the patient of his disease. The extent of the surgery can bear some relation to the degree of malignancy; for example, the superficial facial type of lesion in elderly people does well with only 1–2 cm margin of healthy tissue but in other areas the margin should include up to 5–7 cm of healthy tissue laterally and distally and up to 10–15 cm proximally together with deep fascia.

The defects are covered with split skin grafts which can always be obtained in adequate quantity and act as a 'window' for observation at follow-up examination. Any recurrence should be treated as a matter of urgency and with the same margins of excision as a primary.

Perfusion with cytotoxic drugs of the nitrogen mustard group has a significant effect on melanomas but unfortunately it is only temporary and surgery must still remain the treatment of choice in all except the most advanced cases.

It seems to us, however, that a case can be made out for combining perfusion with surgery in the treatment of primary melanoma of the foot because this site carries such a poor prognosis. There should be about 100 fresh cases of melanoma of the foot each year in England and Wales and if these cases could be directed to two or three special centres then worthwhile progress may be made and valuable data be made available in five years.

The following papers were also read:

The Normal Melanocyte and its Distribution
Professor J D Boyd (*Cambridge*)

The Surgery of Malignant Melanoma
Mr A K Monro (*London*)

Section of Surgery

President
Professor Lambert C Rogers CBE VRD FRCS

Meeting February 1 1961

Short Papers

Inadvertent Parathyroidectomy

by R S Murley MS FRCS and
P M Peters DM (*London*)

Our preoccupation with this problem stemmed from the chance finding of parathyroid tissue on the specimen from a patient who had progressed uneventfully after partial thyroidectomy. In contrast to this we had known tetany to occur in a number of patients whose operation specimens had shown no trace of parathyroid tissue after careful search. Although parathyroid tissue had rarely been recognized on operation specimens in our laboratory it was felt that specific search might well bring more parathyroids to light.

Since August 1, 1954, the pathologists have undertaken a detailed search of all thyroid operation specimens passing through the Group laboratory with the object of revealing every possible scrap of parathyroid tissue. The objects of this investigation were twofold: (1) to determine the incidence of what has now been termed 'inadvertent parathyroidectomy'; (2) to ascertain the relationship to post-operative tetany.

Material: Most of the operations were done at the Royal Northern Hospital and the remainder at two other hospitals in the Group. The Royal Northern specimens came from both the general theatres and the private wing. A number of different surgeons were responsible for these operations.

Laboratory search: Naked-eye identification of parathyroid tissue in the laboratory, though often easy, can be difficult. Approximately 70% of the parathyroids found have been identified in this way. In about 40% of specimens on which the pathologist suspected parathyroid tissue he failed to confirm it on microscopy. Classically yellowish or brownish, the parathyroids are sometimes concealed in fat, lymphoid tissue, thyroid, or even in contiguous thymus. Sequestered thyroid nodules, lymph nodes, fragments of congested fat and thymic remnants may all resemble parathyroids.

Operative search: The surgeon should be able to identify much parathyroid tissue with reasonable certainty. He has the advantage over the pathologist of seeing the living and relatively undisturbed

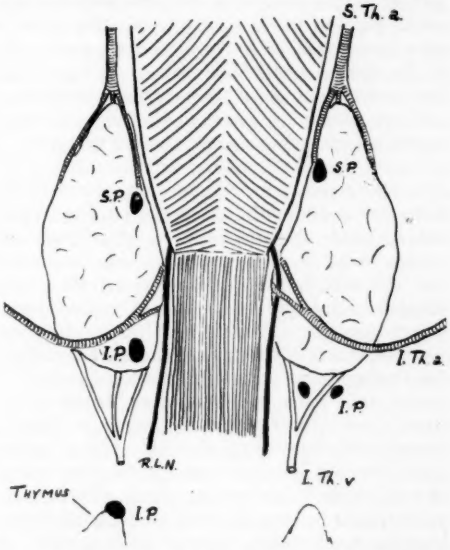


Fig 1 *Lateral lobes of thyroid seen from behind to show position of parathyroid glands (much simplified from Gilmour, 1938). In 74% of cases the superior glands (S.P.) are situated on the posterior border of the middle third of the thyroid as seen on the left. In a further 10% the superior glands are related to the upper third of the thyroid as on right. About 60% of inferior parathyroids (I.P.) are situated as on left, and in 13% they lie with tributaries of the inferior thyroid vein. Much less often an inferior parathyroid is related to thymus. S.Th.a., superior thyroid artery. I.Th.a., inferior thyroid artery. I.Th.v., inferior thyroid vein, recurrent laryngeal nerve*

anatomy of the operation site, but he suffers the disadvantage that he should not usually subject suspicious tissue to histological section. Glands concealed in fat or other tissue will be missed, but inadvertent removal of such concealed glands can often be avoided by thoughtful handling of suspect and potentially risky sites.

The vascularity of parathyroids is well known and pinching the very margin of suspect tissue with fine dissecting forceps can assist identification. In mentioning this test one must strongly deprecate its facile use since extensive contusion of parathyroids may ensue.

Anatomy: The gross anatomy of the parathyroid glands in the cadaver was carefully studied and fully reported by Gilmour (1938). In about 90% of cases there are 4 parathyroid glands. In the remaining 10% the number varies from 2 to 6 or more. Despite the possible wide variations in the position of these glands described by Gilmour, the majority of parathyroid tissue is situated at well-defined sites (Fig 1). The superior glands tend to lie close to the posterior division of the superior thyroid artery; the higher they are the greater is the possibility of inclusion with the upper poles of the resected thyroid. The inferior parathyroids may be at the back of the lower pole of the thyroid, immediately below the lower pole amongst tributaries of the inferior thyroid vein, and sometimes in contact with or concealed within thymic or sequestered thyroid tissue.

Operative precautions: The most important operative steps in avoiding inadvertent parathyroidectomy include the following: (1) Full exposure which, in most cases, should include freeing of the sternomastoids and division of the strap muscles. (2) Ligation of inferior thyroid vein tributaries close to the thyroid. (3) Critical inspection of the back of the upper pole before resection. (4) Peeling back the thyroid capsule at known parathyroid sites and wherever suspect parathyroid or 'fatty' tissue is seen. (5) Careful scrutiny of sequestered thyroid nodules before their removal. (6) Avoiding removal of contiguous lymphoid and thymic tissue. (7) A gentle technique to avoid undue trauma, especially when applying hæmostats to thyroid tissue or stitching the gland remnants.

With these facts firmly in mind the surgeon might anticipate that removal of parathyroids would be a rare occurrence but this study has proved otherwise.

Analysis of specimens: In the first five years of this investigation 332 thyroid specimens were examined, 46 of which included parathyroid tissue. Two parathyroid glands were present on 5 of the 46 specimens (Table 1). The various case records are not sufficiently complete to allow the precise extent of the thyroid resection to be determined for the whole series. However, these details are given in Table 3 for a personal series of cases.

Table 1

Inadvertent parathyroidectomy. Royal Northern Group. August 1954-July 1959 inclusive

Total thyroid specimens examined	332
Number with parathyroid tissue	46
41 specimens included one parathyroid	
5 specimens included two parathyroids	
Incidence of inadvertent parathyroidectomy	13·9%
Tetany recorded in 5 cases	

The relatively high incidence of inadvertent parathyroidectomy was certainly surprising. One of us (R S M), despite the exercise of what was felt to be considerable care, gained the impression that he was removing at least as many parathyroids as everyone else. But further analysis (Table 2) showed that the proportion of parathyroids in this personal series was lower than in the group as a whole. No credit is claimed for these figures since, of all the surgeons taking part, only the surgical author was aware of the investigation.

Table 2

Inadvertent parathyroidectomy. Comparative incidence in personal series and rest of group

Surgeon	*Cases*	*Parathyroid tissue*	*Incidence*
R S M	142	14	9·9%
Others	190	32	16·8%
Total	332	46	13·9%

The personal series included in Table 3 covers a longer period than the whole series. Each of the case notes in the personal series includes a sketch with precise measurements of the resected gland and residual tissue. Any parathyroids seen in the neck are marked on the sketch as are details of accidentally detached and reimplanted glands, of which there were three in this group. The incidence of parathyroid removal and tetany in relation to different types of operation is shown in Table 3, the commonest procedure being bilateral partial thyroidectomy. The term subtotal thyroidectomy is avoided since it is sometimes applied to what we regard as an ill-advised and super-radical resection in which mere buttons of thyroid tissue are left. This analysis is offered as a simple factual record and not because it justifies any significant deductions about the relative hazard of different procedures. In this particular series there does not seem to have been any greater hazard from the more extensive operations.

Transient tetany occurred in 3 cases of the personal series, one of which included a parathyroid on the specimen. Though these 3 cases of tetany occurred in toxic patients it is interesting to note that parathyroidectomy occurred more often in non-toxic cases. The incidence of inadvertent parathyroidectomy remains about the same in the larger personal series (Table 3) since it includes 2 cases in which deliberate marginal biopsy of suspect tissue was done to convince sceptical assistants.

In the personal series of cases the position of the parathyroids on the specimens is recorded as follows: Lower pole 8 cases; upper pole 3 cases; no site specified 6 cases (4 of these were only found in histological sections); biopsy 2 cases (both inferior glands). The inferior parathyroids are therefore more at risk than the superior ones.

Table 3
Type of resection in relation to parathyroidectomy and tetany

Type of resection	*Cases*	*Parathyroid present*	*Transient tetany*
Bilateral partial	118 (44)	13	3 (only one with parathyroid)
Partial one side, hemi other side	28 (3)	2	0
Hemithyroid	23 (2)	4	0
Partial one side	3	0	0
Whole thyroid	6	0	0
Total cases	178 (49)	19●	3 (all toxic)

This personal series covers a slightly longer period than Tables 1 & 2
Figures in parenthesis indicate toxic cases.
● In 2 of the 19 cases a deliberate biopsy of the edge of a suspect gland was done.

Conclusions: Inadvertent parathyroidectomy is much more common than is generally appreciated. The high incidence in this series is, we believe, better attributed to the zeal of the pathologists than the clumsiness of the surgeons. Most of the subjects of inadvertent parathyroidectomy suffer no apparent tetany or other penalty from gland removal. Indeed, tetany often occurs in the absence of parathyroidectomy when it is usually transient and presumably due to bruising of parathyroids. That tetany is more common after operations for toxic goitre is probably due to the greater vascularity of the thyroid and other local peculiarities in such cases.

The practical lesson to be learnt from this research is that, despite the exercise of considerable care at operation, inadvertent removal of parathyroids is not uncommon. It rarely causes serious trouble, but it is clearly a hazard which, together with rough handling of parathyroids, every surgeon should try to reduce to a minimum. That care in this connexion is important is shown by the recent publication by Painter (1960) of figures from one hospital in which a 13% incidence of *permanent tetany* is recorded following 46 operations for toxic goitre. It is further underlined by our own observation at one hospital of a thyroidectomy specimen which included four parathyroids from a patient who suffered bilateral recurrent nerve palsy as well as permanent tetany.

Acknowledgments: We desire to express our sincere thanks to Dr Harold Caplan who was responsible for the pathological examination of a large number of operation specimens.

REFERENCES
Gilmour J R (1938) *J. Path. Bact.* **46**, 133
Painter N S (1960) *Brit. J. Surg.* **48**, 291

Clinical Experiences of the Lesser Known Manifestations of Hyperparathyroidism

Arnold S Aldis FRCS (*Cardiff*)

Generalized osteitis fibrosa cystica as described by Friedrich von Recklinghausen is a rare disease, but its clinical features are so striking, and its pathology so distinctive, that the condition is familiar to every medical student. So also is the fact that the condition is due to a tumour of the parathyroid glands and this has led some to the false conclusion that tumours of the parathyroids must be equally rare, for it is not sufficiently appreciated that hyperparathyroidism due either to hypertrophy or tumours of the parathyroids may produce many other symptoms than those of osteitis fibrosa cystica. This would be of little consequence if these other symptoms were always associated with diagnostic bone changes of von Recklinghausen's disease, but this is not the case, for hyperparathyroidism may result in serious and even fatal disease without producing any clinical or gross radiological evidence of bone lesions. When all these conditions which may result from hypertrophy of tumours of the parathyroids are taken into account they can no longer be regarded as rare, and their recognition is important for they are both serious and at the same time eminently treatable, at least in their earlier stages.

It is the purpose of this paper to draw attention again to some of the ways in which parathyroid tumours may present other than with the classical picture of von Recklinghausen's disease, and which have been encountered in a small series of patients seen and treated in Cardiff. The importance of parathyroid tumours in the genesis of renal calculi is now sufficiently well recognized to

exclude this subject from the present paper, although some still seem to regard even this well-proven association as of more academic than practical import.

The first mode of presentation of a parathyroid tumour to which I would like to draw your attention is the condition of *Pitressin-resistant diabetes insipidus*. We have had 3 such patients in our series and in none of them were there any obvious bone changes. The first of these patients to be seen was perhaps the most striking and his story will serve as an illustration of the condition (Case 1). In passing it is of interest that probably the first case of osteitis fibrosa cystica ever to be described, exhibited this symptom at one stage of the disease. I refer to the description of 'An Extraordinary Case in Physick' made by Dr Thomas Cadwalader of Philadelphia in 1745 and sometimes wrongly attributed to Dr Silvanus Bevan who communicated the account of the case in the *Philosophical Transactions* of the Royal Society in 1743: 'The wife of one B.S. in the year 1738 was taken with a Diabetes with the usual symptoms, viz. a frequent and copious discharge of urine, a gradual wasting of the body &c.'

Case 1 A man aged 37, a winding engineman in a coal mine, was admitted in April 1955. His main symptoms had been extreme thirst and polyuria which had been present for two years, and which had been accompanied by a loss of weight of nearly 3 st, and by anorexia, constipation and occasional vomiting. He had been in the habit of taking large bottles of water to work with him and in addition used to drink up to four pints of milk daily, and even with this excessive fluid intake was sometimes so thirsty that he would drink water out of puddles in the street. When admitted he was severely dehydrated and his tongue was so dry he could hardly speak. He was transferred to the Cardiff Royal Infirmary from another hospital where he had been admitted as a case of diabetes insipidus which, however, was found to be completely resistant to Pitressin. His serum calcium values ranged from 15·8 to 17 mg/100 ml. The mean daily volume of urine was just under ten pints; it was always dilute, with a sp. gr. between 1002 and 1004. On May 18, 1955, a parathyroid adenoma buried in the lower pole of the right thyroid lobe was removed. In the following day he passed only 8 oz of urine of a sp. gr. of 1011. In subsequent days he passed volumes which varied between 2 and 4 pints. In five days he had gained some 10 lb in weight and in three months he had fully regained his weight and was back in full work and has continued well since (Fig. 1).

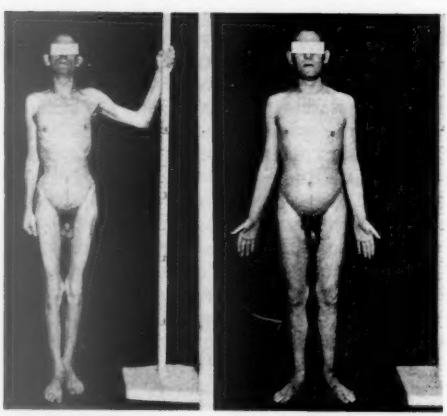


Fig 1 *Patient before and two months after removal of parathyroid tumour.* A, *21.4.55, weight 44·9 kg.* B, *21.6.55, weight 70 kg*

The thirst and polyuria which are the presenting symptoms in such cases have been the subject of much speculation and do not seem to be fully understood as yet. It is probably the direct effect of the hyperglycæmia rather than of the parathyroid hormone or hormones, as similar cases have been described in other conditions in which there is a raised serum calcium, such as sarcoidosis and vitamin-D poisoning. It seems also that, although in late cases organic renal damage may play a part, in early cases the effect is physiological rather than structural, as it disappears immediately the parathyroid tumour is removed.

My second type of presentation is the *solitary osteoclastoma*, illustrated by the following story:

Case 2 A married woman, aged 50, was admitted to hospital on April 11, 1959, complaining of pain in the lower end of the left femur for nine months and an obvious and increasing swelling in the same site for three months. On examination there was an obvious bony tumour of the lower end of the femur and the radiological appearance suggested that this might be a secondary carcinomatous deposit. X-rays of the rest of the skeleton were, however, normal and a biopsy of the bone tumour was reported unequivocally as a Grade 1 osteoclastoma. The patient's blood calcium was found to be in the range 11·7 to 12 mg/100 ml. On July 4, 1959, a parathyroid adenoma was removed from behind the lower pole of the right lobe of the thyroid. Following this the calcium fell promptly to 9·5 mg/100 ml but in spite of this the tumour continued to grow rapidly and a further biopsy was carried out as it was feared that it might have undergone malignant change, but once again a definite report of Grade 1 osteoclastoma was obtained. Since this time the patient has received radiotherapy from the cobalt unit and extensive orthopædic treatment.

The failure of the osteoclastoma to respond to removal of the parathyroid tumour was a disappointment as it had not been appreciated that a prolonged osteoclastic stimulation by parathormone might result in a true tumour which would be self-sustaining and propagating even when the

stimulus was removed. Normally the cysts of osteitis fibrosa cystica regress and recalcify, albeit slowly, after removal of the parathyroid adenoma but there is ample precedent for the idea of prolonged endocrine stimulation producing true tumours in the appropriate end organ. There is of course another possible explanation of the rather disappointing response of this patient, and that is that she may be harbouring a further parathyroid adenoma. Some weight is perhaps given to this possibility by the fact that the osteoclastoma has responded poorly to radiotherapy with very indifferent recalcification and by the fact that although there was a prompt fall in the blood calcium to normal levels, it has risen at the last estimation to the extreme upper limit of normal, 10·7 mg/100 ml. The patient is being brought back into hospital for reassessment from this point of view. An osteoclastoma is normally a tumour of adolescence or young adult life, and the appearance of a solitary osteoclastoma in a patient in the later age groups as in this patient should raise the suspicion of a parathyroid tumour as the cause.

My next patient illustrates again the presenting solitary osteoclastoma but in addition provides yet another possible presenting symptom.

Case 3 A single woman, aged 54, attended hospital first in May 1957 complaining of an increasing tumour of the vault of the skull for two years. This had been accompanied by headaches and some dimness o vision and a gradual personality change, and there had been three epileptiform fits in the two years that the tumour was growing. She also gave a history of several episodes of epigastric pain and vomiting for three years. She attended at the neurosurgical outpatients and was found to have a bony tumour near the bregma which X-ray showed to be an osteolytic tumour of bone and it was thought that it might represent a hyperostosis over an underlying meningioma (Fig 2). However, carotid angiograms gave no evidence of such an underlying lesion and the tumour of the skull was accordingly excised and was reported as a Grade 1 osteoclastoma. The patient next attended at another hospital a year later complaining of epigastric pain and vomiting and a barium meal carried out there revealed two very large gastric ulcers very atypically placed on the greater curvature of the stomach (Fig 3). A partial gastrectomy was carried out. The surgeon expressed the opinion that the ulcers were malignant but the histology was reported as simple chronic gastric ulcer. The suspicion of malignancy was, however, raised again during her convalescence when she developed a post-operative chest complication and an X-ray of her chest was reported as showing small osteolytic metastases in the clavicle and one rib. While attending the outpatient follow-up clinic after this operation the patient slipped and fell injuring her left tibia. A lump developed in the bone at the site of injury and a biopsy of this lesion showed it to be a typical cyst of osteitis fibrosa cystica; and the diagnosis was at last made and confirmed by biochemical investigation.

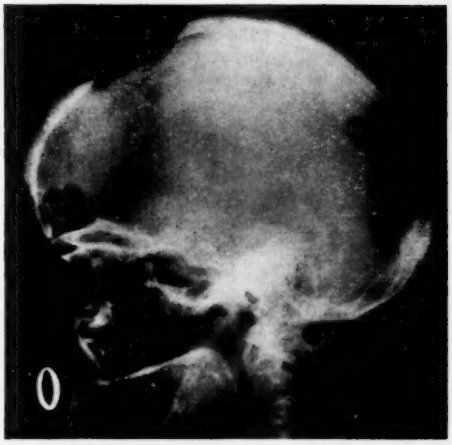


Fig 2 *Radiograph showing osteoclastoma of skull*

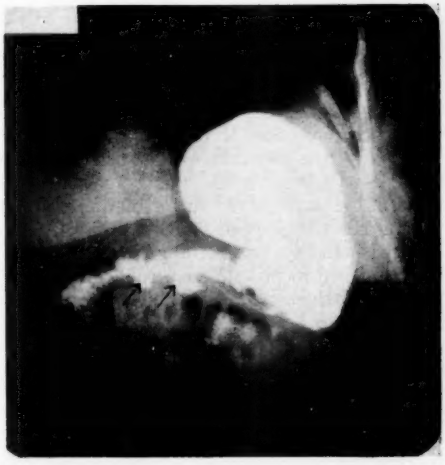


Fig 3 *Barium meal demonstrating two large gastric ulcers (arrowed) on the greater curve*

The patient refused further operative treatment until renal failure was far advanced and finally died shortly after her parathyroid tumour was removed.

The association of peptic ulcers with hyperparathyroidism has been reported by many authors such as Rogers *et al.* (1947) and St Goar (1957). No explanation of this association has been forthcoming and although it is known that when the blood calcium falls below a critical level of about 7 mg/100 ml the secretion of acid by the stomach ceases, there is no good evidence that a high blood calcium is accompanied by an increased

secretion of acid by the stomach. Ostrow *et al.* (1960) suggest that the incidence of peptic ulcer in patients with hyperparathyroidism is very little higher than in the rest of the population, but certainly the literature contains the record of many striking cases and in the patient I have described the ulcers were both multiple and large and most atypically placed on the greater curve.

In conclusion, I would like to mention a recent case in which the patient did not suffer from a parathyroid tumour, but which illustrates that hypercalcæmia may cause acute or chronic pancreatitis. (The patient was a woman of 50 with multiple myeloma and a blood calcium of 22 mg/100 ml who died of acute pancreatitis.) It is true that pancreatitis is more likely to be a terminal rather than a presenting symptom but the association is I think important. It is interesting in this connexion that the first case of multiple endocrine tumours including parathyroid adenomas reported by Erdheim in 1903 probably died of this complication as at autopsy the patient was found to have a necrotic pancreas. Some 8 cases of acute pancreatitis complicating hyperparathyroidism have been reported in the literature.

It seems likely that a high ionic calcium facilitates the conversion of inactive trypsinogen as secreted by the pancreas into active proteolytic ferment trypsin and that this is probably the cause of the pancreatitis. The method of this conversion is a complicated one and is furthermore hedged about by a number of protective mechanisms designed to prevent such conversion occurring in the pancreas. The subject has recently been reviewed with experimental work by Haverback *et al.* (1960), and it is probable that such conversion is most likely to occur in those patients in whom the blood calcium is very high.

These are some of the ways in which parathyroid tumours may present apart from the classical bone changes of von Recklinghausen's disease and an awareness of these possibilities will I believe lead to a more frequent diagnosis of these tumours and their surgical removal at a stage before they have caused irrevocable damage to the patient.

REFERENCES

Bevan S (1743) *Phil. Trans.* **42, 488**
Cadwalader T (1745) An Essay on the West India Dry Gripes, to which is added an extraordinary case in physick. Printed and sold by Benjamin Franklin, Philadelphia
Erdheim J (1903) *Beitr. path. Anat.* **33, 158**
Haverback B S, Dyce B, Burdy H & Edmondson H A (1960) *Amer. J. Med.* **29, 424**
Ostrow J D, Blanshard G & Gray S J (1960) *Amer. J. Med.* **29, 769**
Rogers H M, Keating F R jr, Morlock C G & Barker N W (1947) *Arch. intern. Med.* **79, 307**
St Goar W T (1957) *Ann. intern. Med.* **46, 102**

DISCUSSION

Professor C E Dent (*London*) congratulated Mr Murley on his excellent surgery as well as on his paper. On the medical side many patients were seen with permanent hypoparathyroidism following surgery to the thyroid, but he had no figures to indicate how often this complication occurred. He asked Mr Murley how far he was able to do blood tests for Ca and P on his patients post-operatively. Professor Dent had often observed the remarkable individual variation in sensitivity to hypocalcæmia, some patients with plasma Ca as low as 5 mg/100 ml showing none of the ordinary signs and symptoms of tetany. One could not therefore exclude hypoparathyroidism without blood tests. Such patients were likely to present later with other complications, often psychiatric, sometimes with epilepsy, usually after fifteen years or so with cataract.

With regard to Mr Aldis's paper Professor Dent stressed the increasing number of patients with primary hyperparathyroidism whose diagnosis had been made accidentally. As in several other series of cases in the literature they had often been led to note renal stones only while doing X-rays for other purposes; in one patient the bone changes were noted first on mass radiography of the chest. In addition to these, however, there were 8 patients in their series of 67 to date at University College Hospital in whom neither osteitis fibrosa nor renal stones were present. These 8 were detected after the plasma levels were determined for quite the wrong reasons such as misinterpretation of X-rays. He stressed this here as he thought this must mean that primary hyperparathyroidism was a fairly common disease. They should therefore maintain a high index of suspicion and be prepared to arrange investigations on only minimal clinical or other indications. The obvious first thing to do was to estimate the plasma Ca and P.

Mr. Murley, in reply to Professor Dent, stated that post-operative estimations of Ca and P had been done in all cases for a short period. Several patients had shown an early fall in Ca which was occasionally quite marked. None of these people had developed obvious tetany. He had not done routine Ca and P estimations in all cases at follow-up, but the patients had been subjected to critical clinical assessment. He did, however, entirely agree with Professor Dent that hypoparathyroidism could not certainly be excluded without blood tests.

(*Meeting to be continued*)

Section of Medicine

President E R Cullinan MD

Meeting January 24 1961

Hypoproteinæmia in Gastrointestinal Disease [*Abridged*]

by A M Dawson MD and Roger Williams MD
(*London*)

Hypoalbuminæmia in disease may be due to a decreased synthesis of the protein or to an increased rate of destruction. In gastrointestinal disease the importance of decreased synthesis has been stressed. This may be due either to impaired digestion, absorption or metabolism of protein precursors, but little attention has been given to the possible role of increased catabolism. Recently, evidence has started to accumulate which shows that in fact synthesis is often normal or even slightly increased and destruction rapid (Citrin *et al.* 1957, Schwartz & Jarnum 1959, Gordon 1959, Steinfeld *et al.* 1960). First I shall discuss how standard methods of investigating protein metabolism in man may help to assess the relative importance of these two factors. The use of the nitrogen balance technique in clinical investigation is now well established and for the sake of this argument I shall merely consider the excretion of fæcal nitrogen as compared with the oral intake. For example, in a patient with severe small bowel disease and impaired absorption of protein one might expect an excretion of 5 g of fæcal nitrogen a day (normal <2 g); this is equivalent to 31·25 g of protein. The daily needs of the body may be generously put at 45 g and so a total of 76·25 g of protein would be needed to maintain a patient in balance. In fact, this is a normal dietary intake. Moreover many patients with hypoalbuminæmia in gastrointestinal disease do not even have a raised fæcal nitrogen. Thus theoretically, impaired digestion and absorption of protein products is an unlikely cause of hypoalbuminæmia unless dietary intake is very low.

By using ^{131}I-labelled albumin, the albumin synthesis has been shown to be normal or slightly increased, in a variety of gastrointestinal disorders, while destruction is often accelerated, but such data do not give a clue to the site of the increased degradation. One might suspect this site to be the diseased gastrointestinal tract and this has been demonstrated by direct intubation of the stomach in patients with giant rugal hypertrophy (Citrin *et al.* 1957) and intubation of the intestine in small bowel disease (Holman *et al.* 1959). In both these studies excessive albumin was shown to be leaking into the gut lumen. Presumably the leaking protein is digested and the peptides and amino acids so formed are reabsorbed so that the fæcal nitrogen is not raised. Similarly if albumin ^{131}I is used as a tracer for the serum protein, it leaks into the gut lumen, is broken down and the water-soluble radioactive products are reabsorbed so that negligible radioactivity appears in the fæces. The reason that hypoproteinæmia occurs at all is that the liver has a limited reserve in its ability to synthesize albumin.

The measurement of albumin turnover with simultaneous intubation of the bowel would be far too tedious for a routine clinical test. Gordon (1959) has partially overcome this problem by introduction of the use of polyvinylpyrrolidone (PVP) labelled with ^{131}I. When injected intravenously this substance, which has a similar molecular weight to that of albumin, can leak through similar sites to those which are permeable to albumin; in this case into the gastrointestinal tract. However, PVP is relatively inert to the digestive enzymes and so can escape into the fæces and there the radioactivity may be measured. The test is performed by injecting this substance intravenously after blocking the patient's thyroid with iodine, and then collecting the stools and urine separately for 4 consecutive twenty-four-hour periods; great care is taken to prevent contamination of the fæces with urine. Twenty-one patients with a variety of gastrointestinal disorders were also studied; these included idiopathic steato-

Metabolic Disorders in Gastrointestinal Disease

rrhœa (4), cryptogenic steatorrhœa (2), jejunal diverticulosis (2), ulcerative jejunitis (1), idiopathic hypoproteinæmia (2), giant rugal hypertrophy of the stomach (1), ulcerative colitis (2), polyarteritis nodosa (1), secondary amyloidosis (1), pancreatic steatorrhœa (1), total gastrectomy (1), Crohn's disease (1), scleroderma (1), biliary enteric fistulæ (1). Three patients with cirrhosis and 2 with a nephrotic syndrome (all of whom had a low serum albumin) as well as 18 normal persons who had neither disorders of the gastrointestinal tract nor abnormalities of their plasma proteins were also studied. In Fig 1 is shown the serum albumin of these patients with gastrointestinal disease plotted against the fæcal excretion of ^{131}I PVP, the mean excretion being 0·52% with a range of $<$0·05 to 1·6%. With decreasing serum albumin levels there is a tendency to an increased fæcal PVP. Taking the lower limit of serum albumin as 3·5 g/100 ml only one patient with a low albumin level had a normal PVP excretion. This man had a total gastrectomy and a very poor dietary intake and severe steatorrhœa; it is possible that this hypoalbuminæmia is purely nutritional in origin. On the other hand 4 patients with a normal serum albumin had a slightly raised PVP excretion. Apart from these patients the results were remarkably consistent. That such an overlap was observed is to be expected on at least three counts: (*a*) PVP, although similar in size to albumin, is not the same as the albumin molecule – the shape and the charge on the molecule are different. (*b*) Serum albumin does not necessarily reflect total body stores of albumin. (*c*) Gastrointestinal protein loss is probably intermittent so that such a loss may not be occurring during the test. Hypoalbuminæmia itself does not cause an increased loss of PVP, for 2 patients with a nephrotic syndrome and 3 with cirrhosis, all with hypoalbuminæmia, were found to have a normal excretion; similarly 4 patients with diarrhœa not associated with hypoalbuminæmia had a normal PVP excretion.

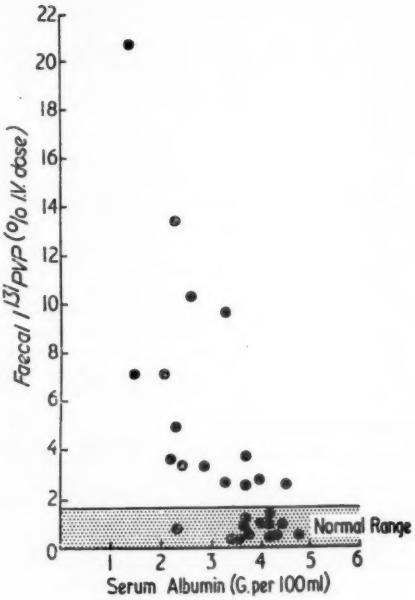


Fig 1 *Serum albumin plotted against ^{131}I PVP excretion in patients with gastrointestinal disease and idiopathic hypoproteinæmia. Hatched area represents normal range of PVP excretion*

We have studied 6 patients on more than one occasion (Table 1). In all these patients during the active phase of the disease when they had hypoalbuminæmia the fæcal excretion of PVP was

Table 1
Serial studies with ^{131}I PVP

Patient	*Age*	*Sex*	*Diagnosis*	*Serum albumin g/100 ml*	*Fæcal ^{131}I PVP % I.V. dose*	*Remarks*
1	43	M	Giant rugal hypertrophy of stomach	3·7 4·3	2·6 0·4	 After subtotal gastrectomy
2	53	F	Idiopathic steatorrhœa	3·3 4·8	9·7 0·5	 Gluten-free diet
3	56	F	Idiopathic hypoproteinæmia	2·6 3·3	10·3 2·7	
4	38	F	Regional ileitis	2·2 3·4	3·6 0·1	Active Quiescent
5	16	M	Cirrhosis and ulcerative colitis	3·5 2·4 4·2	0·05 3·4 0·4	Pre-colitis Active colitis Quiescent colitis
6	26	M	Ulcerative colitis	2·8 4·2	3·4 0·5	Active Quiescent

raised, while during a remission or following treatment there was a rise in serum albumin and an associated fall in the fæcal excretion.

These results support the view that protein leakage into the intestine, rather than impaired digestion and absorption, is often a dominant cause of hypoproteinæmia in a variety of gastrointestinal diseases. Further, in the occasional patient with hypoproteinæmia of unknown cause a careful search of the gastrointestinal tract must be made; this should include a ^{131}I PVP test, a small bowel biopsy and sometimes even laparotomy.

Acknowledgments: We should like to thank the physicians of The Royal Free Hospital for allowing us to study their patients and all others who have referred patients to us.

REFERENCES
Citrin Y, Sterling K & Halstead J A (1957) *New Engl. J. Med.* 257, 906
Gordon R S jr (1959) *Lancet* i, 325
Holman H, Nickel W F jr & Sleisenger M H (1959) *Amer. J. Med.* 27, 963
Schwartz M & Jarnum S (1959) *Lancet* i, 327
Steinfeld J L, Davidson J W, Gordon R S jr & Green F E (1960) *Amer. J. Med.* 29, 465

Hæmatological Abnormalities

by Clifford F Hawkins MD FRCP (*Birmingham*)

Hæmatological changes may be due to deficiency of iron, folic acid or vitamin B_{12} (cyanocobalamin); and, also, to the inflammation which involves the bowel wall in colitis or Crohn's disease. Only the megaloblastic anæmias will be considered here, for this is where a break-through in our knowledge has taken place. In the past, most cases have been labelled 'pernicious anæmia'. Accurate techniques for studying fæcal fat excretion first encouraged separation of anæmia due to disease of the small intestine from true addisonian pernicious anæmia. The discovery of folic acid and vitamin B_{12} then stimulated methods of investigation which now allow cases of deficiency of B_{12}, of folic acid, or of both, to be distinguished.

Addisonian pernicious anæmia, a genetically determined disease resulting in atrophic changes in the gastric mucosa, can be regarded as the prototype of B_{12} deficiency. The patients are usually over 40 years old, but rare examples have been described in children. One boy suffered from lack of Castle's intrinsic factor but had a normal flow of hydrochloric acid and a normal gastric mucosa (Mollin *et al.* 1955); his father had pernicious anæmia with complete gastric atrophy. It is possible that pernicious anæmia is one of the diseases due to a specific enzyme deficiency. A congenital lack of intrinsic factor may result in prolonged subclinical B_{12} deficiency which causes the gastric atrophy. Iatrogenic pernicious anæmia follows total gastrectomy.

Another cause of B_{12} deficiency is the fish tapeworm, *Diphyllobothrium latum*. It absorbs radioactive B_{12} in preference to its host and so may compete for this vitamin. However, only a small number of infested persons develop the anæmia; it is thought that the anæmia is more likely if the worms are in the jejunum, but there is some evidence that the worm itself may cause a gastric atrophy (Siurala 1956).

More important in this country is the B_{12} deficiency due to anatomical lesions of the small intestine such as strictures, fistulæ, blind loops and diverticula of the small bowel. The common factor is stagnation or contamination of the small gut. Modern investigations and the use of antibiotics have vindicated the views of the older writers in indicting the bacteria as the cause. There is evidence that the coliform bacteria compete for B_{12} and so deprive the host of it (Doig & Girdwood 1960) but it is also possible that metabolites of the bacteria – the toxins of the older writers – could interfere with the absorption or utilization of B_{12} (Drexler 1958). This type of megaloblastic anæmia is rare and only occurs in a small percentage of patients with these bowel lesions. Corrective surgery may cure the anæmia (Watkinson *et al.* 1959). To-day it is seen particularly in Crohn's disease with fistula or blind loop formation. When one reads the autopsy reports of the tuberculous strictures of the bowel described earlier this century (Meulengracht 1932) it seems that many to-day would be regarded as Crohn's disease. Crohn's disease, when it causes anæmia, usually does so from iron deficiency, but B_{12} deficiency may occur from extensive involvement of the ileum (Meynell *et al.* 1957). Folic-acid deficiency is seen in the malabsorption syndromes, such as idiopathic steatorrhœa and tropical sprue, where the disease affects the jejunum. B_{12} deficiency may be present in up to half the cases; this may be due to extension of the disease to the jejunum, or possibly to bacterial contamination of the small bowel. The evidence suggests that folic acid is absorbed mainly in the jejunum and B_{12} in the ileum (McIntyre *et al.* 1956, Meynell *et al.* 1957, Booth & Mollin 1959).

Addisonian pernicious anæmia and the malabsorption syndrome have occurred in about equal numbers in a series of 61 unselected patients with megaloblastic anæmia admitted to The General Hospital, Birmingham (Bradley & Cooke

1960). Thirty-one cases were due to pernicious anæmia, 27 to idiopathic steatorrhœa, 2 resulted from operations on the alimentary tract, and 1 was due to drugs. The more complete the investigations, the less frequent is the diagnosis of pernicious anæmia. Cases of idiopathic steatorrhœa can often be collected by going through the files of patients labelled pernicious anæmia and investigating them more fully. The clinical picture of megaloblastic anæmia from either B_{12} or folic acid deficiency may be indistinguishable, but the presence of neurological lesions supports B_{12} deficiency. (The malabsorption syndrome occurs at any age and there may be multiple vitamin deficiencies; malnutrition is more likely, and many patients suffer from diarrhœa. Accustomed to mild diarrhœa over a long period, patients may reply 'yes' to the question 'Are your bowels normal?'; further questioning reveals a bowel movement three or more times daily. The appearance of the stool on the fingerstall or in the sluice often allows an immediate diagnosis of steatorrhœa. Further investigations, such as analysis of fæcal fat excretion (Kamer *et al.* 1949), radiological studies, and jejunal biopsy using the Crosby capsule (Crosby & Kugler 1957), are usually necessary to establish an exact diagnosis. The serum vitamin B_{12} level is helpful (Mollin & Ross 1954), as it is the first sign of B_{12} deficiency, occurring before macrocytosis or other changes in the blood. Tests of folic acid absorption and excretion are avoided initially as they involve treatment with folic acid, which confuses the response to the gluten-free diet.

For the patient with idiopathic steatorrhœa, the gluten-free diet offers the best hope of restoring the health and blood to normal (French *et al.* 1957). The anæmia of idiopathic steatorrhœa is usually macrocytic and slight, but the most striking example of the effect of this treatment is seen in the severe megaloblastic anæmia which is identical to pernicious anæmia and may be fatal. When gluten is withdrawn, a reticulocytosis occurs but is later and smaller than after folic acid. A rapid rise in the hæmoglobin and red cells takes place until the blood values, including the mean corpuscular volume, are entirely normal. Conversion of the marrow from megaloblastic to normoblastic occurs within a month without hæmatinics or other therapy. Iron deficiency may be unmasked and delay cure of the anæmia; then oral iron can be given as it appears to be absorbed normally in those responding to the diet. Dr J M French and I find that 34 out of 48 patients (71%) with idiopathic steatorrhœa have responded successfully. Fat excretion and other tests of intestinal function are normal in most, but sometimes power to absorb fat and folic acid is not restored in spite of apparent clinical and hæmatological cure. The jejunal mucosa, like the gastric mucosa in pernicious anæmia, fails to return to normal. The blood picture remains entirely normal while the patient is on the diet and this has been so in all successful cases, many of whom have been followed up regularly for six years or more. Response to the gluten-free diet is probably connected with the folic acid deficiency as vitamin B_{12} levels may be normal or low; if low, it may take up to a year before normal levels are reached. It is curious that a rapid response in the blood may precede any improvement in the fat excretion or other tests. It is not possible to predict which patients will respond and the trial may have to go on for three or six months. A course of antibiotics has, in an occasional patient, seemed suddenly to aid response to the diet.

When the megaloblastic anæmia is so severe as to threaten life it may be necessary to give a hæmatinic immediately, before a definite diagnosis has been made. Most megaloblastic anæmias respond temporarily to folic acid but it is usually preferable to know exactly which deficiency exists and then it is best to give a single injection of vitamin B_{12}. The fall in serum iron after forty-eight hours will give a quick indication of the response (Hawkins 1955) and the reticulocyte count can then be followed if necessary. If there is no fall in serum iron folic acid can be given. Folic acid is dangerous in pernicious anæmia as it may precipitate a severe neuropathy due to the dwindling reserves of vitamin B_{12} being used for the formation of blood, but this risk does not seem to be present in idiopathic steatorrhœa even when a B_{12} deficiency exists as well.

There are, then, two main groups, pernicious anæmia and idiopathic steatorrhœa. But is each a single entity with a single cause, or will the future show a breakdown of each group with different ætiologies? I suspect the latter. It is not known why some cases of idiopathic steatorrhœa fail to respond to withdrawal of gluten although the clinical picture, jejunal mucosa and autopsy appearances are identical with others which do. We are, at present, studying a man aged 31 with gout who also had a megaloblastic anæmia due to folic acid deficiency. A jejunal biopsy showed blunting of the villi with changes in the epithelial cells; the nuclei of these were swollen in some, and in others there were particles resembling nuclear remnants. The appearances were similar to those produced in the intestinal mucosa of rats by Leblond & Stevens (1948). These workers used colchicine to arrest mitosis in order to estimate 'turnover time' of the intestinal epithelium. My patient had been taking colchicine daily for at

least ten years and it is possible that the changes were also due to this drug, and that the megaloblastic anæmia had followed the damage to the jejunal mucosa. Further work has been planned in the hope of proving this hypothesis.

REFERENCES
Booth C C & Mollin D L (1959) *Lancet* i, 18
Bradley J & Cooke W T (1960) Personal communication
Crosby W H & Kugler H W (1957) *Amer. J. dig. Dis.* 2, 236
Doig A & Girdwood R H (1960) *Quart. J. Med.* 29, 333
Drexler J (1958) *Blood* 13, 239
French J M, Hawkins C F & Smith N S (1957) *Quart. J. Med.* 26, 481
Hawkins C F (1955) *Brit. med. J.* i, 383
Kamer J H van de, Huinink H ten Bokkel & Weijers H A (1949) *J. biol. Chem.* 177, 347
Leblond C P & Stevens C E (1948) *Anat. Rec.* 100, 357
McIntyre P A, Sachs M V, Krevens J R & Conley C L (1956) *Arch. intern. Med.* 98, 541
Meulengracht E (1932) *Acta med. scand.* 78, 387
Meynell M J, Cooke W T, Cox E V & Gaddie R (1957) *Lancet* i, 901
Mollin D L, Baker S J & Doniach I (1955) *Brit. J. Hæmat.* 1, 278
Mollin D L & Ross G I M (1954) *Proc. R. Soc. Med.* 47, 428
Siurala M (1956) *Acta med. scand.* 154, 337
Watkinson G, Feather D B, Marson F G W & Dossett J A (1959) *Brit. med. J.* ii, 58

Effects of Malabsorption Syndrome on Calcium Metabolism

by B E C Nordin MD MRCP PhD (*Glasgow*)

The malabsorption syndrome causes specific secondary effects on the endocrine glands, on the hæmopoietic system and on calcium metabolism. The secondary effects on calcium metabolism take the form of osteoporosis (i.e. reduced bone mass), osteomalacia (i.e. inadequate calcification of bone) or tetany or any combination of these three. Some idea of the relative incidence of these complications may be obtained from Table 1 which shows that 11 out of 21 cases of steatorrhœa, mostly of the 'idiopathic' variety, were found to be suffering from complications involving calcium metabolism, mainly spinal osteoporosis. Conversely the screening of 56 cases of osteoporosis and 14 of osteomalacia disclosed 8 cases of steatorrhœa among the former and 11 cases of steatorrhœa among the latter (Table 2). It would appear from these data that osteoporosis is a relatively common complication of steatorrhœa, and that steatorrhœa is in turn the commonest cause of osteomalacia in this country at the present time.

Table 1
Disorders of metabolism in ... of steatorrhœa

Osteoporosis	6
Osteomalacia	3
Osteoporosis & osteomalacia	1
Osteoporosis & tetany	1
No abnormality	10

Table 2
Steatorrhœa in 70 cases of metabolic bone disease

	Osteoporosis	*Osteomalacia*
Steatorrhœa	8	11
No steatorrhœa	48	3
Total	56	14

Investigation and Diagnosis
The investigation of calcium metabolism in a case of steatorrhœa requires in the first instance X-rays of the hands, femur and lumbar spine and certain biochemical tests on the blood and urine. These procedures can be performed on outpatients and will usually provide most of the necessary information. Further investigation in hospital, which may be necessary in difficult cases or because of the patient's clinical condition, consists in carrying out the four-hour retention test, iliac crest biopsy and possibly a calcium balance. These procedures will be considered in turn.

Bone X-rays: The bone X-ray procedure described by Barnett & Nordin (1960) involves standard measurements on X-rays of the hands and femur and on a lateral view of the lumbar spine. Reduction in the thickness of the cortex of the femur or metacarpals is indicative of peripheral osteoporosis. Biconcavity of the lumbar vertebral bodies (which is best determined on a lateral tomogram of the lumbar spine) is usually associated with accentuated vertical trabeculation of the vertebræ and indicates spinal osteoporosis. These two forms of osteoporosis may co-exist. We do not at present understand the clinical significance or pathogenesis of peripheral osteoporosis and all the cases of osteoporosis which we have so far discovered in association with steatorrhœa have been spinal or mixed.

The radiological features of osteomalacia are rather different. The pathognomonic feature is the pseudo-fracture or Looser zone which may be seen in the cortex of a long bone or in the pelvis. Alternatively there may be cancellization of the cortex, i.e. the femoral cortex is as thick as usual but less homogeneous, as though there was patchy failure of mineralization within the compact bone. The spine X-rays may be relatively normal or there may be a curious haziness of the vertebral bodies which looks like a technical artifact but which is probably a genuine feature of the condition. The radiological features of osteoporosis may be present in addition, signifying that the two conditions are present at the same time.

Biochemistry: The first step in the biochemical investigation of these cases is to obtain a random urine sample together with a blood sample preferably obtained near the midpoint of this urine collection. Calcium, inorganic phosphate and creatinine are measured in the plasma and urine and the alkaline phosphatase in the plasma. This procedure permits the measurement not only of

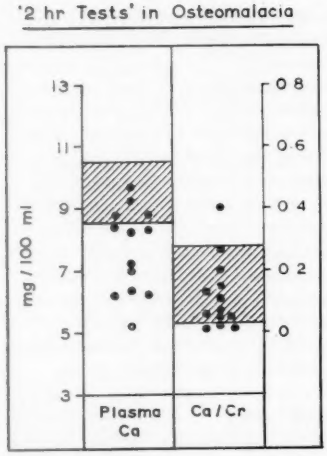


Fig 1 *Plasma calcium and urinary calcium/creatinine ratio in 13 cases of osteomalacia. The shaded area shows the normal range*

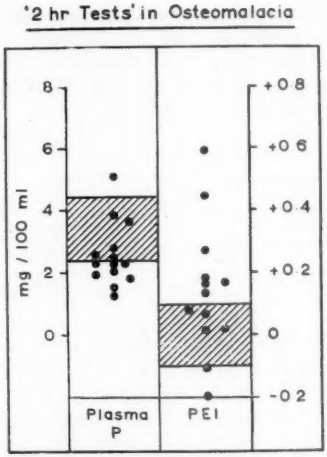


Fig 2 *Plasma phosphorus and phosphate excretion index (P.E.I.) in 13 cases of osteomalacia*

the plasma levels of calcium, phosphorus and alkaline phosphatase but also of the urinary calcium/creatinine ratio and the phosphate/creatinine clearance ratio. In simple osteoporosis all these values are normal with the possible exception of the urinary calcium/creatinine ratio which may be low, normal or high.

Table 3
Biochemical data in osteomalacia

	Ca	*P*	$[Ca]^3 \times$		*Phosphate excretion*	*Alkaline*
Normal range in adults	*(mg%)* (9·0–10·5)	*(mg%)* (2·5–4·5)	$[P]^2$ (4,600–20,000)	*Ca/Cr* (0·03–0·28)	*index* (–0·09–+0·09)	*phosphatase (K-A units)* (10–14)
Steatorrhœa						
T H	6·2	2·8	1,880	0·07	+0·09	65
I F	7·2	2·6	2,600	0·01	+0·17	11
E D	8·8	2·5	4,250	0·13	+0·18	26
J B	6·2	2·0	960	0·14	+0·02	11
I W●	6·3	3·9	3,800	0·07	–0·10	44
J N●	8·4	3·8	10,200	0·10	+0·02	20
J M	8·4	1·6	1,600	0·05	+0·14	20
B S	5·2	1·4	260	0·02	+0·30	14
M H	7·0	1·9	1,240	0·20	+0·60	50
M M	8·4	2·4	3,450	0·27	+0·08	24
No steatorrhœa						
A B●	9·7	6·2	26,500	0·01	–0·20	49
M W	9·2	2·1	4,400	0·06	+0·45	13
R N	8·8	2·4	3,250	0·27	+0·08	24

●adolescent

The biochemical results obtained in 13 cases of osteomalacia (10 associated with steatorrhœa) are shown in Figs 1 & 2 and Table 3. In the typical case of osteomalacia there is a reduction in the plasma levels of calcium and particularly of phosphate, and an abnormally low product $[Ca]^3 \times [P]^2$ (Nordin 1960). The urinary calcium/creatinine ratio may be low but is more frequently normal; the only case in this series in which it was actually raised was one of biliary cirrhosis with steatorrhœa in which the plasma citrate level was raised; this may explain the hypercalciuria. The phosphate excretion index (P.E.I.) (Nordin & Fraser 1960) is raised and can be restored to normal by the intravenous infusion of calcium (Nordin & Fraser 1954). The plasma alkaline phosphatase is raised. Table 3 shows that certain cases did not fulfil all these criteria, particularly cases I W, J N and A B. These were all adolescents with rickets, two of them associated with steatorrhœa and one with dietary vitamin-D deficiency.

The four-hour retention test: If the preliminary investigation does not establish the diagnosis beyond all reasonable doubt, or if the patient is in hospital for other reasons, the four-hour calcium retention test (Finlay *et al.* 1956) provides very reliable information. It is simple to perform and invariably gives a high calcium retention figure in osteomalacia. It may be possible to diagnose osteomalacia with this technique at an earlier stage than is possible with the other procedures.

Iliac crest biopsy: It is rare for iliac crest biopsy to be an essential investigation, but it is frequently highly desirable. Comparison of the amount of bone in a standard biopsy sample with a 9-point scale enables the diagnosis of osteoporosis to be made with some degree of confidence (Beck & Nordin 1960). In cases of steatorrhœa two samples should be obtained and one of them cut without decalcification for assessment of the osteoid borders the enlargement of which is the diagnostic characteristic of osteomalacic bone.

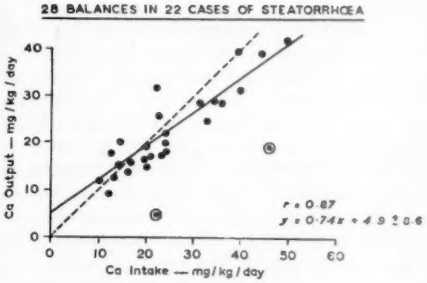


Fig 3 *Relation between calcium intake and ouput in 28 balances in 22 cases of steatorrhœa. (Note: circled values not included in statistical analysis)*

Calcium balance: The purpose of a calcium balance is to provide information about the patient's ability to absorb calcium. It is a lengthy and costly procedure but until some satisfactory isotopic technique has been perfected it is the only available method. Fig 3 shows the result of 28 calcium balances in 22 cases of steatorrhœa. At all levels of intake cases of steatorrhœa tend to be in slightly more negative or less positive calcium balance than normal subjects on the same intake. This is entirely due to the difference in fæcal calcium, which tends to be slightly higher in cases of steatorrhœa than in normal subjects. However, the slope of the regression of output on intake is parallel with that of normal subjects, indicating that some degree of positive balance can be achieved in steatorrhœa if the calcium intake is high enough. No consistent difference has been observed between the calcium absorption of cases of steatorrhœa with osteoporosis and those with osteomalacia, although it is true that the osteomalacia group do include the cases with the highest fæcal calcium output. The mean calcium requirement of the cases shown in Fig. 3 (i.e. the value of intake at which intake and output are equal) is 18·9 mg/kg as compared with the normal mean requirement of 9·3 mg/kg.

Pathogenesis

(*a*) *The cause of the osteoporosis:* The association of osteoporosis and steatorrhœa is entirely compatible with the hypothesis that spinal osteoporosis is due to prolonged negative calcium balance (Nordin 1960). If calcium balance is a function of the relationship between intake, absorption and excretion then malabsorption of calcium would tend to produce negative calcium balance. This negative balance may result from a very high fæcal calcium, explained by the trapping of digestive juice calcium in the gut, or it may be the result of persistent normocalciuria in the face of an inadequate calcium absorption. The great majority of our cases of osteoporosis with steatorrhœa have a normal urinary calcium excretion and not the low urine calcium which would be required if they were to remain in calcium balance in the face of inadequate calcium absorption.

The cause of the malabsorption of calcium in steatorrhœa is uncertain but it has at various times been attributed to vitamin-D deficiency and to the formation of insoluble calcium soaps. Nassim *et al.* (1959) however, have shown convincingly, that the malabsorption of calcium in steatorrhœa with osteomalacia cannot be corrected even by parenteral vitamin-D but responds to a gluten-free diet and we have found the same to be true in steatorrhœa with osteoporosis. The malabsorption of calcium does not therefore appear to be due to vitamin-D deficiency.

If the malabsorption of calcium were due to calcium soap formation one might expect to find some quantitative relationship between the amount of fat and the proportion of ingested calcium excreted in the fæces. Fig 4 shows that there was little or no relationship between these two measurements in 146 balance periods on 17 cases of steatorrhœa with osteomalacia and/or osteoporosis. This does not appear to support the idea that calcium malabsorption is due to calcium soap formation.

It is more probable that the malabsorption of calcium in steatorrhœa is a direct reflection of the alimentary disorder which is also responsible for the malabsorption of fat. When this basic disorder is corrected (as with a gluten-free diet in

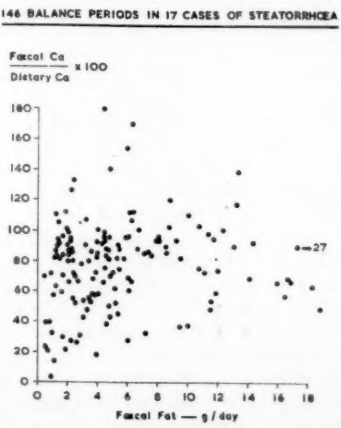


Fig 4 *Relation between fæcal fat and fæcal calcium (expressed as a percentage of dietary calcium) in 17 cases of steatorrhœa*

idiopathic steatorrhœa) calcium absorption improves together with the absorption of other minerals and vitamins.

(*b*) *The cause of the osteomalaica:* The osteomalacia of steatorrhœa is probably due to vitamin-D deficiency rather than to malabsorption of calcium. It is well established that vitamin D acts directly on the skeleton to sustain the plasma calcium concentration and that this effect on plasma calcium is quite independent of the effect of vitamin D upon calcium absorption (Carlsson & Lindquist 1955, Nordin 1960). Deficiency of vitamin D therefore leads to a fall in plasma calcium which usually stimulates the parathyroid glands and so causes hypophosphatæmia and a raised phosphate clearance, which is reflected in a high P.E.I. Occasionally, however, the parathyroid glands fail to respond – reflecting perhaps the general impairment of endocrine function in steatorrhœa (Mickerson 1960) – and this leads to tetany. Tetany and osteomalacia may co-exist if the rise in plasma phosphate in these cases is insufficient to offset the effect of the reduced plasma calcium on the $[Ca]^3 \times [P]^2$ product (Nordin 1960).

In the light of these general observations the various abnormalities and disturbances of calcium metabolism which occur in steatorrhœa can be explained in the following way. Simple malabsorption of calcium produces negative calcium balance and osteoporosis. Vitamin-D deficiency leads to abnormalities in the plasma biochemistry and consequently to osteomalacia and/or tetany. The combination of malabsorption of calcium with abnormal biochemistry produces the combined syndrome of osteoporosis and osteomalacia which is not uncommonly seen in malabsorption states.

Therapy

This explanation is supported by the fact that vitamin-D therapy given in the form of ultraviolet light corrects the biochemical disorder of osteomalacia without having any demonstrable effect upon calcium absorption (Nordin 1960). One month of ultraviolet light therapy restores the $[Ca]^3 \times [P]^2$ product to normal. We have seen complete radiological healing of rickets within two or three months and very considerable improvement in the state of the femoral cortex after a rather longer period. The beneficial effect of a course of ultra-violet light appears to last about one year in uncontrolled steatorrhœa, but if the steatorrhœa can be controlled with a gluten-free diet or by other means it is probable that small oral doses of vitamin D can then be given as maintenance therapy.

We are not sure how the osteoporosis should be treated. The balance data suggest that some improvement in calcium balance can be obtained by feeding calcium supplements, but this improvement is not nearly so impressive as the improvement in calcium balance obtained with calcium supplements in osteoporosis without steatorrhœa. In the present state of knowledge it is probably advisable to give calcium supplements in a dose of about 1 g of calcium daily above the patients' ordinary diet. This can conveniently be given as calcium glycerophosphate 6 g daily.

REFERENCES

Barnett E & Nordin B E C (1960) *Clin. Radiol.* **11**, 166
Beck J S & Nordin B E C (1960) *J. Path. Bact.* **80**, 391
Carlsson A & Lindquist B (1955) *Acta physiol. scand.* **35**, 53
Finlay J M, Nordin B E C & Fraser R (1956) *Lancet* i, 826
Mickerson J N (1960) *Brit. med. J.* i, 529
Nassim J R, Saville P D, Cook P B & Mulligan L (1959) *Quart. J. Med.* **28**, 141
Nordin B E C (1960) *Clin. Endocrin.* **1**, 233
Nordin B E C & Fraser R (1954) *Clin. Sci.* **13**, 477
(1960) *Lancet* i, 947

Section of Odontology

President R V Bradlaw CBE FRCS FDS RCS

Meeting February 27 1961

Short Papers

The Influence of Drugs on Bleeding

by C Wishart BDS FDS RCS LDSEd (*Salisbury*)

Bleeding is the most obvious and immediate reaction to laceration of the tissues and it is not surprising that civilized man has continually sought for suitably potent medicaments whose contact with a wound would rapidly arrest hæmorrhage and promote healing. Medical literature from ancient times contains references to a great variety of these nostra, some few of which are possibly useful, but most have only an adverse effect. Birch & Snider (1939) compiled a list of over fifty of these drugs with reputed hæmostatic effect, including such substances as persulphate of iron, silver nitrate, oil of ergot and powdered rice. White of egg was the choice of many, and muscle of dove was once recommended, perhaps for its content of tissue thromboplastin. Their list may sound fanciful but there is sometimes a sound pharmacological basis for the use of some of the long-established folk-medicines. For example, a preparation made from the dried and powdered skin of the common toad, known as Ch'an Su, has been used for many centuries by the Chinese as a hæmostatic agent, especially for the treatment of bleeding gums. Only in recent times has it been demonstrated that the toad's skin is particularly rich in epinephrine.

The Hæmostatic Agents

Hæmostasis is not the same thing as coagulation of shed blood but there are some indications for the use of styptics and hæmostatics. The three preparations in this group most commonly used in oral surgery are Russell's viper venom, thrombin and fibrin foam.

The venom of the Russell viper acts in the nature of an extremely powerful thromboplastin and is even active in a concentration of 1 : 20,000,000 (MacFarlane & Barnett 1934). For this reason it has been used as perhaps the favourite of all topical drugs in the treatment of localized superficial bleeding in hæmophiliac patients (Cambrook 1936). On account of its specific action as a thromboplastin it is of value in the treatment of defects of coagulation arising from deficiency of Factors V, VII, VIII, IX and X.

Both bovine and human thrombin are available in powder form or as a liquid. Bovine thrombin does not seem to produce marked antigenic reactions but there are reports of the transmission of homologous serum hepatitis by human thrombin. Fibrin foam and gelatin sponge are particularly suitable vehicles for solutions of thrombin.

Oxidized cellulose and calcium alginate are both prepared in the form of a gauze and are both regarded as absorbable hæmostatics. They act by providing a matrix with a large surface area on which shed blood may clot. Cellulosic acid also reacts directly with hæmoglobin but its low pH inactivates thrombin and may interfere with healing, particularly in bone.

Adrenaline may be used in conjunction with any of these drugs and when applied topically to mucous membrane or skin it acts directly on effector cells resulting in intense vasoconstriction. To some extent this response depends upon the concentration of adrenaline at the site and in dilution it can have a positive vasodilatory action on superficial vessels. The congestion of mucosa which may follow its use is partly accounted for by this phenomenon. Adrenochrome monosemicarbazone, which is a metabolite of adrenaline, has been introduced in recent years as an agent for increasing capillary tone and thus enhancing the efficiency of the hæmostatic mechanism, but as yet there is no clear evidence that it is of clinical value.

Antihæmophilic globulin (AHG) has been isolated from bovine and porcine blood (MacFarlane *et al.* 1954, Bidwell 1955). This is of very high potency and is of great value given intravenously, in the control of hæmophiliac bleeding but in its present form is strongly antigenic. Nevertheless it has been used successfully in major surgery and for dental extractions (Fraenkel & Honey 1955, MacFarlane *et al.* 1957). More recently Kekwick & Wolf (1957) have used purified

human AHG which is nonantigenic but this material is scarce and its use is therefore scarcely justified in oral surgery where adequate transfusions of fresh frozen plasma will temporarily correct the clotting defect.

General Anæsthetic Agents

Apart from these drugs which may help to control bleeding there are many which may have an indirect effect. It is a matter of everyday experience that all patients tend to bleed more freely when anæsthetized. Even premedication with morphine causes relaxation of the cutaneous blood vessels and most general anæsthetic agents depress the vasomotor centre. Ether, chloroform and cyclopropane are particularly notable for this effect. On the other hand, powerful hypotensive agents may be used in the so-called 'lytic' cocktail (promethazine HCl, pethidine, chlorpromazine and diethazine) to reduce hæmorrhage to a minimum.

The use of a local anæsthetic with epinephrine in conjunction with a general anæsthetic has a sound pharmacological basis. Not only does the adrenaline cause vasoconstriction but the interruption of the pain pathways prevents the immediate rise in blood pressure which otherwise occurs at the first stimulus of an operation.

The Iatrogenic Group

During the first half of this century, with the development of pharmacology as a precise study, a large number of new drugs was introduced, some of which gave rise to serious toxic effects causing depression of the hæmopoietic system and allergic purpura. For their pharmacological value in the treatment of various conditions some of these have been retained in practice to this day, so that their use by patients who require to undergo dental extractions may complicate treatment. Drugs which may result in prolonged and serious hæmorrhage are apronal (Sedormid, allylisopropyl-acetyl-carbamide), gold, the sulphonamide group, chlorpromazine and many others. Ackroyd (1949, 1954), in extensive studies of this phenomenon in the case of apronal, concluded that in some patients an antigenic apronal/platelet complex is formed in the presence of complement. The antibodies produced have the capacity to lyse platelets and also have a toxic effect on the capillary endothelium, resulting in severe thrombocytopenic purpura.

Most, if not all, of the therapeutically useful members of the sulphonamide group and streptomycin and chloromycetin have been found to give rise to similar toxic effects, although the incidence must be low in view of the extent to which they have been used since their introduction (Macauley 1954). The platelet level may not fall below that at which spontaneous hæmorrhage might be expected, but there is in most recorded cases a marked effect upon the integrity of the capillary walls. Even a single topical application of sulphathiazole ointment can cause severe purpura, although this is much more likely if two separate courses of the drug are given (Sherlock & White 1944). One of the more recently introduced sulphonamides, sulphamethoxypyridazine, is now accumulating its own bibliography and there have been reports during the past year of a number of fatal cases associated with severe thrombocytopenic purpura (Green & Finkel 1959, Cohlan 1960).

Gold and phenylbutazone, both used in the treatment of rheumatoid arthritis, may cause a secondary thrombocytopenia (Short *et al.* 1946). One in four patients on gold therapy shows some reaction, and one in two hundred dies from it, usually as a result of a profound thrombocytopenia. Such patients should therefore have a full blood examination before any surgery.

A less serious interference with hæmostasis may arise from the local use of penicillin in high concentration. This was pointed out by Fleming & Fish (1947) who concluded from their *in vitro* experiments that such use should be limited to the flushing out of a wound with a solution not exceeding 100 units per ml in strength. Moldavsky *et al.* (1945) and Macht (1947), on the other hand, reported that systemic penicillin may shorten the clotting time.

Aspirin is probably the commonest of all drugs in use today and may be taken regularly and in quite high dosage. It can result in a hypoprothrombinæmia and is therefore anticoagulant. The mechanism by which it produces this effect is not known, although it is more likely to do so in patients whose intake or synthesis of vitamin K is deficient.

The Steroids

The steroids may of themselves produce a hypercoagulability of the blood with a thrombotic tendency. Pharmacologically, however, their most important effect on bleeding is their capacity to improve the hæmostatic mechanism in essential and secondary thrombocytopenia. Cortisone may induce a remission of chronic leukæmia and it may temporarily raise the platelet count in a case of essential thrombocytopenia. It can be of value therefore if dental extractions have to be undertaken in such cases, but its effect should be checked by platelet counts and Hess tests before, during, and after surgery.

The Anticoagulants

A new iatrogenic disorder was introduced in 1936 when heparin was first used as a prophylactic

anticoagulant by both Murray and Crafoord (Goodman & Gilman 1955) and since the first use of bishydroxycoumarin in 1941 (Meyer *et al.* 1942, Butt *et al.* 1941). Anticoagulants are used to prevent or delay intravascular clotting and are of value in post-operative venous thrombosis and in reducing the incidence of coronary thrombosis. There is conclusive evidence that short-term anticoagulant therapy reduces the mortality from myocardial infarction but the position of long-term anticoagulant therapy is still not finally established.

A working party of the Medical Research Council reported (1959) that high-dosage long-term anticoagulant therapy significantly reduced the reinfarction rate, particularly in males under the age of 55. It is therefore likely that the dicoumarin group of drugs will be used to an even greater extent than heretofore, for some time to come, as a means of reducing the incidence of myocardial infarction. With these patients we are concerned for they may present considerable difficulties in treatment.

Whereas heparin can actually prevent clotting, bishydroxycourmarin and its congeneric substitutes such as phenidione and ethyl biscoumacetate decrease the coagulability of the blood in a rather complex way. Administration of the dicoumarin drugs primarily causes a fall in the available Factor VII and secondarily depresses the level of prothrombin. Indirect evidence tends to show that its effect is achieved by interfering with the role of vitamin K in the liver synthesis of prothrombin. There is also evidence that Factor IX and Factor X are depressed (Owren 1959, Verstraete *et al.* 1957). The extent of the effect of the dosage on the individual is usually measured by Quick's one-stage prothrombin time. Although this is the control test in most common use it has the disadvantage that it does not sensitively reflect the decrease in coagulability and more refined and better standardized tests will no doubt be introduced.

Different congeners of bishydroxycoumarin are available, some of which are short-acting and some long-acting. With the short-acting drugs it may be difficult to maintain a constant level with the result that the prothrombin time fluctuates, but the usual aim is to maintain this at approximately two and a half times the normal. At such a level the patient is not in a hæmorrhagic state in the sense that spontaneous hæmorrhage will occur, but tissue damage at this level is undoubtedly liable to lead to prolonged bleeding. Nevertheless, the clotting mechanism is still effective although delayed, the platelets are unaffected, and the blood vessels and capillaries unaltered. Minor trauma is therefore unlikely to present a great problem with regard to hæmostasis. Severe trauma on the other hand presents a medica emergency and must be treated without delay with vitamin K and blood transfusion if necessary. Douglas & Brown (1952) and Toohey (1954) have shown the value of vitamin K_1 as an antidote and this takes effect within a few hours.

It is clear that patients on anticoagulants must be handled with care if surgery becomes necessary. It has been suggested that it is necessary to modify the administration of anticoagulants to prevent bleeding following dental operations (*J. Amer. med. Ass.* 1958) and Hallam (1961) has adopted this policy with successful results. He withdraws anticoagulants until the prothrombin level is 60% of normal, extracts the teeth, and recommences anticoagulant therapy twenty-four hours later. In his patients there has been no instance of thrombosis or of excessive hæmorrhage.

Toohey (1958), on the other hand, states that major surgical procedures have been carried out on full anticoagulant therapy and that with dental extractions there is no need for cessation of treatment. Honey (1961) recommends that anticoagulant therapy be maintained during dental extractions and the prothrombin level kept to 15% to 20% of normal. Nevertheless this only applies to simple extractions where no great surgical damage is expected. Stafford (1960) also recommends that there should be no interruption of anticoagulant therapy prior to dental extractions. This policy is well supported by the observations of Sevitt & Gallagher (1959) who found no marked increase in bleeding from patients on phenindione who underwent orthopædic operations for fracture of the femur. Extractions should of course be carried out with care and the operator should be prepared to deal with any ensuing hæmorrhage by the normal local measures. The fitting of a splint to protect the formed clot in the sockets is a useful precaution and topical hæmostatics such as thrombin and fibrin foam may here be expected to be of some value.

An increased risk of thrombosis is laid upon a patient if anticoagulant drugs are suddenly withdrawn, and it would seem unwise to withdraw the potential protection during a time of increased stress represented by the incident of tooth extraction.

Aspirin, which is such a useful analgesic drug, is also a thrombopenic agent and therefore enhances the effect of phenindione. It should not be prescribed for sedation for a patient who is on anticoagulant therapy and the sulphonamides should also be avoided (Biggs & MacFarlane 1957). Oral antibiotics are reported to enhance the effect of oral anticoagulants (Toohey 1958) and if there is a place for them at all in the management of dental infections it is not in these cases since they may reduce the intestinal flora

which synthesize vitamin K, and thus upset the effect of the anticoagulant.

Further experience is, however, necessary to determine more precisely the extent to which these patients are at risk during dental surgical operations and what precautions are desirable.

REFERENCES
Ackroyd J F
(1949) *Clin. Sci.* **7**, 249
(1954) *Clin. Sci.* **13**, 409
Bidwell E (1955) *Brit. J. Hæmat.* **1**, 386
Biggs R & MacFarlane R G
(1957) Human Blood Coagulations. Oxford; p 339
Birch C le F & Snider F F (1939) *J. Amer. dent. Ass.* **26**, 1933
Butt H R, Allen E V & Bollman J L (1941) *Proc. Mayo Clin.* **16**, 388
Cambrook J D (1936) *Proc. R. Soc. Med.* **29**, 281
Cohlan S G (1960) *J. Amer. med. Ass.* **173**, 799
Douglas A S & Brown A (1952) *Brit. med. J.* i, 242
Fleming A & Fish E W (1947) *Brit. med. J.* ii, 242
Fraenkel G J & Honey G E (1955) *Lancet* ii, 1117
Goodman L S & Gilman A (1955) The Pharmacological Basis of Therapeutics. 2nd ed. New York; p 1500
Green I & Finkel M (1959) *N. Y. St. J. Med.* **59**, 2034
Hallam J (1961) Personal communication
Honey G E (1961) Personal communication
J. Amer. med. Ass. (1958) **168**, 2081
Kekwick R A & Wolf P (1957) *Lancet* i, 647
Macauley D (1954) *Brit. med. J.* ii, 1269
MacFarlane R G & Barnett B (1934) *Lancet* ii, 985
MacFarlane R G, Biggs R & Bidwell E (1954) *Lancet* i, 1316
MacFarlane R G *et al.* (1957) *Lancet* ii, 251
Macht D I (1947) *Arch. int. Pharmacodyn.* **75**, 26
Medical Research Council (1959) *Brit. med. J.* i, 803
Meyer O O *et al.* (1942) *Amer. J. med. Sci.* **204**, 11
Moldavsky L F *et al.* (1945) *Science* **102**, 38
Owren P A (1959) *Farmakoterapi* **4**, 93
Sevitt S & Gallagher N G (1959) *Lancet* ii, 981
Sherlock S & White J C (1944) *Brit. med. J.* ii, 401
Short C L *et al.* (1946) *New Engl. J. Med.* **235**, 362
Stafford J L (1960) *Dent. Practit.* **10**, 248
Toohey M
(1954) *Brit. med. J.* i, 1020
(1958) *Brit. med. J.* i, 252
Verstraete M, Clark P A & Wright J S (1957) *Circulation* **16**, 213

Erupted Teeth in the Newborn

by J H Gardiner BDS DORTH RCS (*Sheffield*)

Introduction: Periodically, in the medical and dental literature, cases are reported of infants born with teeth already erupted. These are usually noticed as a result of the infant having difficulty in breast feeding. Little is known, however, of the subsequent dental history of these cases. In this communication I shall survey the relevant literature and present the information gained from the periodic dental examination of 12 such cases extending over several years.

Definition: These teeth erupted at birth have been called natal teeth by Massler & Savara (1950) who also refer to teeth erupting during the thirty days after birth as neonatal teeth. In earlier literature the terms used included congenital teeth, fœtal teeth and dentitio præcox.

Historical review: Instances of infants born with teeth have been recorded from very ancient times, such as the cuneiform inscriptions found at Nineveh (Ballantyne 1896). A seventeenth century translation of the Roman writer Pliny the Elder quotes him as follows: 'Certaine it is also that some children are borne into the world with teeth as Manius Curius who thereupon was surnamed Dentatus and Consul Papyrius Carbo, both of them very great men and right honourable personages'.

The belief that a splendid future awaited anyone born with teeth was widely held in France and Italy, possibly because this condition is reported to have occurred in such notable persons as Louis XIV, Mirabeau, Mazarin, Cardinal Richelieu, Napoleon and the anatomist Broca. Shakespeare records in his plays (e.g. Richard III, Act II Sc. 4) the tradition that the English King Richard III was born with teeth such that 'he could gnaw a crust at two hours old'.

Kanner (1928) tells that the Slavonian and Ural-Altaic tribes believe that children born with teeth will become witches or sorcerers and the Kasubians that, after death, they will rise from their graves to suck the blood from their nearest relatives. In Poland and India such children are considered monsters and bearers of misfortune (Massler & Savara 1950) and in parts of Africa they are left to die in the bush. More recently, Allwright (1958) reports from China that these teeth are considered to bring very bad luck to the family; the parents of one infant made strong claims to the tooth when extracted so that it could be deposited, together with its attendant evil spirits, in the middle of Hong Kong harbour! In case, therefore, any of these beliefs have penetrated into our localities, perhaps it is always best, as Charon (1955) advises, to 'reassure the parents'.

Incidence: The frequency of these cases is difficult to establish accurately as detailed pædiatric records are of recent origin. The parish register of Church Broughton in Derbyshire in the year 1767 carries an entry of an infant having 'two teeth cut when born', but possibly pædiatric records are a more fruitful source of information. Even so, the condition could pass unnoticed if feeding were not affected and this may account for the divergence in the figures given.

Ballantyne (1896) was probably the first to make an estimate of the incidence – he found it to be 1 in 6,000. Bodenhoff (1959) in a more recent review of 186 reports in the literature and an investigation of 145 cases reported by Danish midwives and health visitors, places the incidence at at least 1 in 3,000 births. In Britain the incidence would appear to be in the region of 1 in every 2,000 live births.

Comparative anatomy: In the cow, sheep and goat, the lower deciduous incisors are normally erupted before birth and in the horse and pig both upper

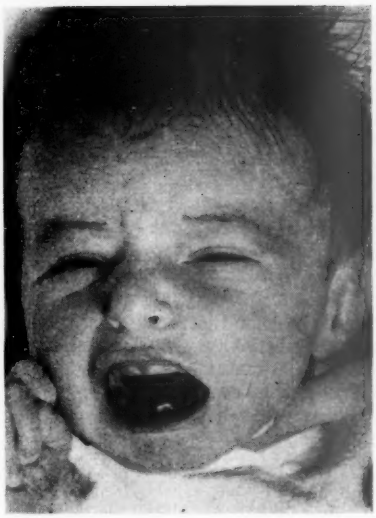


Fig 1 *Child aged 5 days with natal tooth* ($\overline{|A}$)

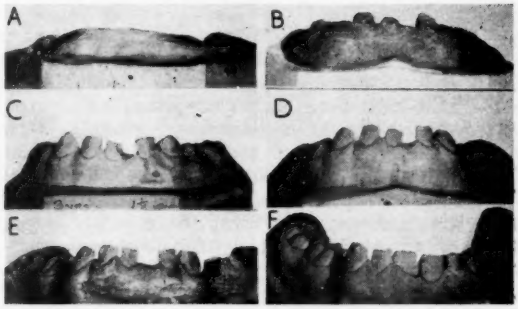


Fig 2 *Models showing the closing of incisal space (measured between* $\overline{B|}$ *and* $\overline{|B}$*) following the loss of* $\overline{|A}$ *and also the opening of this space at 5 years.* A, *aged 4 months – 0 mm;* B, *aged 1½ years – 9 mm;* C, *aged 3 years – 7 mm;* D, *aged 5¼ years – 7·5 mm;* E, *aged 6½ years – 8 mm;* F, *aged 7½ years – 12 mm*

and lower deciduous incisors appear either before birth or during the first few weeks of life (Ellenberger & Baum 1932).

Pre-deciduous teeth: In all the 12 cases from Sheffield, and in most of those in the world literature, the teeth were true deciduous teeth which had erupted prematurely, usually in the lower incisor region. There have, however, been four cases reported in the world literature of what are termed 'pre-deciduous teeth', usually in the lower deciduous molar region. For instance, Allwright (1958) reports upon a Chinese infant in whom, two weeks after birth there erupted in each lower deciduous molar region a small calcified nodule about the size of a grain of rice. They were quite loose and were extracted 10 days later. Neither had roots but the base of each was perforated like the apex of the root of a normal tooth. In their place the normal deciduous lower molars erupted at the usual time.

Clinical appearance: At birth natal teeth (Fig 1) usually appear to be perched upon a pad of soft tissue above gum level whereas the neonatal teeth are covered in a cap of gum tissue. As at this stage in their development only the crown would be formed these teeth are freely mobile and this might explain the inflamed appearance of the ragged tissue around the cervical region.

Histological appearance: Schröder & Moral (1918) studied decalcified sections of a natal tooth with gum tissue attached which had been excised on the eighth day, then stained with hæmatoxylin and eosin. They could not find a continuous enamel layer and they also reported some irregularity in the formation of the dentine near the amelodentinal junction with large interglobular spaces as also reported by Scheff (1911), Howkins (1932) and Hals (1957). Towards the cervical edge of the crown, Schröder & Moral (1918), Boyd & Miles (1951) and Hals (1957) all report finding cells in the dentine. Boyd & Miles give an excellent account of the supporting tissues, because in the case of their specimen, a stillborn fœtus, they were able to section through the complete mandible. They point out that cells are sometimes included in human secondary dentine laid down in response to a sudden injury and suggest that possibly owing to the speed with which the dentine matrix was laid down in this natal tooth, cells or portions of the pulp become incorporated in it. In this connexion it is important to bear in mind that the base of a natal tooth is subject to trauma every time the child moves its tongue or lips, and these movements commence *in utero*, some time before birth. For instance, movements of the arms, legs and trunk have been observed in human fœtuses as early as eight weeks after conception (Fitzgerald & Windle 1942). Swallowing would also seem to occur, for amniotic fluid and any dye introduced has been found later in the infant's gastrointestinal tract (Smith 1959). Béclard (1813) says 'On carefully opening the gravid uterus of a mammal one can clearly see . . . through the amniotic fluid the fetus making mechanical respiratory movements . . . accompanied by an opening of the mouth'.

When examining the pulpal tissue of a natal tooth, Schröder & Moral noticed a small number of hæmorrhages distributed throughout the pulp. This, and the vascularity of the pad of tissue at the base of the crown could possibly also be explained by the constant movement of the crown from tongue and lip pressure.

Ætiology: Over the years there have been many suggestions put forward for the cause of this condition, including hypovitaminosis, hormonal stimulation, febrile states, pyelitis and syphilis. One of the most likely suggestions in my own opinion and that of the more recent writers is the superficial positioning of the tooth germ. Boyd & Miles show this very clearly in their section of the fœtal mandible. There the erupted deciduous centrals were lying, not in a crypt, but in a slight hollow on the surface of the alveolar bone, very much above the germ of their permanent successor.

Why is it that only the lower centrals are in this elevated position? The radiograph of the mandible in Boyd & Miles' paper shows the gap at the symphysis menti where osseous union is not complete until the first or second year after birth (Aitchison 1950); could it be that some anomaly in the symphysis could affect the positioning of the lower central incisor tooth germs in the newborn?

One ætiological factor which is more certain is heredity or familial tendencies. Gates (1946) states 'the condition is probably an irregular dominant, but the irregularity might be due to the presence of an inhibitor or to two genes being required'. Massler & Savara found that 10 out of the 24 cases reported in world literature had siblings or parents with the same condition. Coleman (1914) reports an infant with natal teeth whose sister and father were also born with two lower incisors erupted. Rosenhaupt (1911) described a family in which the eldest son had one natal tooth and the third son three. The children of this latter son had teeth erupting in their second month. Asana (1921) in India reported natal teeth in two children of the same father by different wives. Of the 12 cases in Sheffield, 3 gave a definite family history of natal or neonatal teeth and 4 of the 7 cases reported from the Leeds University Child Health Department gave a definite family history of this condition.

Treatment: The reason often given for extracting these natal teeth is that they may become progressively looser and may be swallowed or aspirated, but as yet no such complication has been reported. A more obvious reason for their removal is ulceration of the undersurface of the tongue as reported by Blaschko (1855). Difficulty in feeding or injury to the mother's nipple is yet another obvious reason for removing these teeth. If neither of these conditions present and the teeth are left to develop then they may even last to the age of 20 (Kennedy 1924).

Magitot (1883) described one case where excessive hæmorrhage followed extraction and proved fatal, but, in reviewing this later, Ballantyne suspected that some condition such as hæmophilia could have been present. Despite the hypoprothrombinæmia in the newborn infant, no other case of excessive hæmorrhage has been reported. Allwright (1958) states that in Hong Kong he extracted 25 natal and neonatal teeth from a total of 15 infants without any special precautions to control bleeding. Similarly in 4 of the 12 Sheffield cases, teeth were extracted without complications ensuing.

Follow-up experience: Of the 8 Sheffield infants who did not have teeth extracted soon after birth, 2 infants shed their natal teeth within a few days and 2 infants at about 3 months. The rest grew as normal teeth until the usual 5½ to 6 years of age when they were shed naturally in 2 cases, but in 1 further case they persisted and had to be extracted to avoid displacing $\overline{1}|\overline{1}$ and in yet another case they persisted due to the absence of $\overline{1}|\overline{1}$.

My fear when I heard of these lower incisors being extracted at birth and saw the resultant space closing, especially when assisted by thumb-sucking activity, was that the lower arch would collapse and there would be insufficient room for the succeeding teeth. This, of course, happens frequently in the deciduous molar region. But despite the space closing initially, at about 5–5½ years of age it began to open again (Fig. 2). In none of the 9 cases where permanent lower incisors have appeared have these been crowded.

Acknowledgments: I would like to record my gratitude to Professor R S Illingworth for bringing this condition to my attention, and for his help and encouragement in preparing these records.

REFERENCES

Aitchison J (1950) Dental Anatomy and Physiology for Students. 2nd ed. London; p 28
Allwright W C (1958) *Brit. dent. J.* **105**, 163
Asana D J (1921) *Indian med. Gaz.* **56**, 16
Ballantyne J W (1896) *Trans. Edinb. obstet. Soc.* **21**, 181
Béclard P A (1813) *Bull. Fac. Méd. Paris* **3**, 436
Blaschko (1855) *Allg. med. ZentZtg* **98**, 778
Bodenhoff J (1959) *Odont. Tidskr.* **67**, 645
Boyd J D & Miles A E W (1951) *Brit. dent. J.* **91**, 173
Charon L F (1955) *Arch. Stomat. Liége* **10**, 272
Coleman F (1914) In: The Science and Practice of Dental Surgery. Ed. N B Bennett. Oxford; p 18
Ellenberger W & Baum H (1932) Handbuch der Vergleichenden Anatomie der Haustiere. 17th ed. Berlin
Fitzgerald J E & Windle W F (1942) *J. comp. Neurol.* **76**, 159
Gates R R (1946) Human Genetics. New York; p 367
Hals E (1957) *Oral Surg.* **10**, 509
Howkins C (1932) *Brit. dent. J.* **53**, 402
Kanner L (1928) Folklore of the Teeth. New York; p 10
Kennedy E C (1924) *Dent. Rec.* **44**, 273
Magitot E (1883) *Brit. J. dent. Sci.* **26**, 640
Massler M & Savara B S (1950) *J. Pediat.* **36**, 349
Pliny G (*circa* A.D. 70) Natural History. Lib vii c.16 in P Holland's translation (1601). London; p 164
Rosenhaupt H (1911) *Arch. Kinderheilk.* **55**, 268
Scheff J (1911) *Öst.-ung. Vjschr. Zahnheilk.* **27**, 1
Schröder H & Moral H (1918) *Dtsch. Mschr. Zahnheilk.* **36**, 97
Smith C A (1959) The Physiology of the Newborn Infant. 3rd ed. Springfield, Ill.; p 42

A Case of Acquired Unilateral Mandibular Condylar Hypoplasia

by P H Burke BDS HDD DDO (*Newcastle upon Tyne*)

The importance of the head of the condyle as the main growth centre of the mandible was first fully realized by Wilson Charles (1925). Its significance in producing facial deformity when there is interference with this growth centre due to trauma or infection has been fully described by Rushton (1944) and Greer Walker (1957).

Case Report

F B, female, now aged 22 years 7 months.

There was no family history of facial deformity. Birth weight and delivery had apparently been normal. She had suffered no injuries or illnesses other than the usual ailments of childhood until the age of 4 years 9 months. At that time she was standing underneath a see-saw and sustained a blow on the right malar region from the descending see-saw. There are no details of the immediate effects of this injury but she later developed a discharge from the right ear.

On examination at the age of 6 years 3 months: Face asymmetrical, chin displaced to the right, left lower cheek region flat, seals lips by contracting mentalis. On opening the mouth no limitation of movement but deviation more marked: left condyle moves normally but right condyle does not pass forward on to eminentia. Facial growth otherwise normal.

Study models showed an Angle's Cl.II arch relationship and the presence of a maxillary overjet of 7·8 mm (Fig 2A). Later records showed a progressive increase in the facial asymmetry, the maxillary overjet and a developing deviation of the mandibular dental mid-line to the right (Figs 1B & 2B).

At the age of 11 years 6 months an oblique lateral mandibular radiograph of the right side showed a rudimentary condylar head and a boss of bone on the inferior surface of the temporal bone. The head of the condyle appeared to be displaced inferiorly and anteriorly, the gonial angle of the mandible appeared less than 90 degrees and the coronoid process was apparently prolonged. In addition to the reduction in vertical height of the ramus the interference in antero-posterior growth of the mandible was shown by the reduction in the distance between second premolar and the posterior border of the ramus. Unerupted in this area were the three permanent molar teeth.

Interpretation of a cephalometric lateral skull radiograph taken at the same age confirmed this displacement of the condylar head downwards and forwards (Fig 3A). The lower border of the body of the right mandible ascended steeply posteriorly and was reduced in length.

A postero-anterior skull radiograph recorded at the same age (11 years 6 months) showed deficient bone growth of the right mandible, the displacement of bony and dental mid-lines with tilting of the incisors to the left and the abnormal form of the right condylar head and neck: the latter was medial and posterior to the coronoid process (Fig 3B). These bony deformities of the mandible agree with the experimental findings of Sarnat & Engel (1951) after excision of the condylar head in the monkey. The inferior surface of the temporal bone was lower on the right side.

At this stage the surgical removal of the right second and third mandibular molar teeth was undertaken by Mr (now Professor) Hopper.

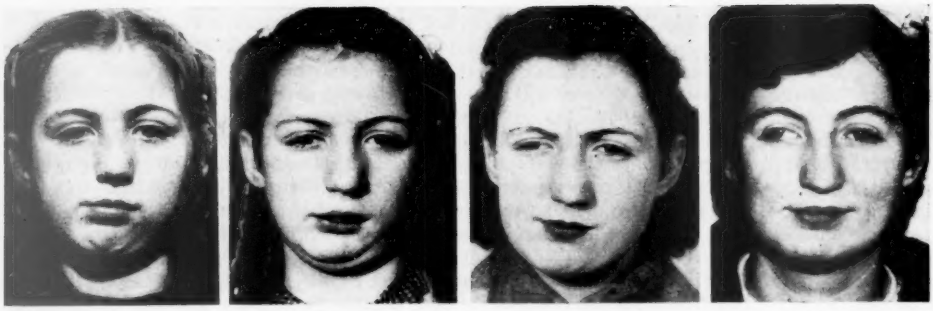
By the age of 13 years 2 months the maxillary overjet was 10·2 mm and the shift of the lower dental mid-line to the right was half the width of the right maxillary central incisor.

Orthodontic treatment was begun at the age of 13 years 6 months. After the extraction of maxillary first premolar teeth, elastic intermaxillary traction was applied using a metal cap splint in the lower arch and a free-sliding labial bow in the upper arch. When the maxillary overjet was reduced to 2·5 mm some seven months later the patient was placed in retention (Fig 2C). All appliances were discarded at the age of 15 years 4 months.

At the age of 16 years 4 months the patient was again referred to Mr Hopper and he and Mr R C Bell carried out an onlay bone grafting operation. A bone graft 2½ in. long and 1 in. deep from the right hip was inserted into a subperiosteal pocket on the lateral aspect of the body of the mandible on the left side. This was intended to be the first stage only of the plastic surgery reconstruction; the second stage was to have been a repositioning of the soft tissues of the chin restoring the mid-line. In the event, when the first stage was completed the patient expressed herself entirely happy with the result obtained by the onlay operation. Mr Hopper therefore confined his treatment to the removal of the remaining unerupted right first permanent molar.

The change in facial appearance between the age of 16 years (after orthodontic treatment and just before the onlay bone graft) and 22 years (six years after the operation) is evident (Fig 1C & D). This patient has suffered a further separate piercing injury of the right eye.

The occlusion has remained stable and the lower dental mid-line is now deviated to the right almost the whole width of the maxillary central incisor (Fig 2D). There is no periodontal disease. A lateral skull radiograph taken at this age, i.e. 22 years, shows clearly the abnormal form and



A B C D

Fig 1 *Facial views at ages 10 years 5 months* (A), *11 years 9 months* (B), *16 years* (C) *and 22 years 7 months* (D)

position of the condylar head and that the formerly steeply inclined lower border of the body of the mandible on the right side is now normally inclined to the face and the deficiency in length is not so pronounced (Fig 3C).

When this tracing is superimposed on the tracing of the radiograph taken at 11 years, using the landmarks 'sella' (S) and 'nasion' (N) for orientation, the extent of the growth and treatment changes can be appreciated (Fig 3D). The apparent absence of growth changes affecting the left mandible is explained by the compensatory adjustment of bone from the normal to the deficient right side across the mid-line thereby causing deviation of the bony and, to a lesser degree, the dental mid-lines. It would therefore appear that in this patient only a partial interference has occurred in the pattern of growth of the condylar head on the right side.

Fig 2 *Study models at ages 8 years 8 months* (A), *12 years 6 months* (B), *15 years 4 months* (C) *and 22 years 7 months* (D)

Comment

A point of interest is the decision regarding the timing and nature of the surgical treatment and its integration with the orthodontic treatment. The alternatives are:

(1) To restore the mandibular dental base to at least its correct relationship with the maxillary dental base by osteotomy and bone-grafting operations in the mixed dentitional stage so that the permanent dentition can take up a satisfactory occlusion.

(2) To accept the dental base relationship and carry out orthodontic treatment in the mixed or permanent dentition to be followed by surgery in the form of masking operations such as epithelial inlays or onlay bone grafts.

Some of the factors to be considered when making this decision are:

(*a*) Severity of the damage to the head of the condyle – severe injury will favour the first course.

(*b*) The age of the patient at the time of injury. Low's (1952) serial growth data suggested that the greatest increment of mandibular growth occurs in the first year of life. Thus if injury occurs at birth or during the first year the interference in mandibular growth will be maximal and masking operations may be less effective. Rushton (1944) and Greer Walker (1957) emphasized that a further age factor is the vulnerability of the condyle to crush injuries which the latter author believes is pronounced up to the age of 6 years.

(*c*) The potential for facial growth of the patient. With our present inadequate serial data on facial

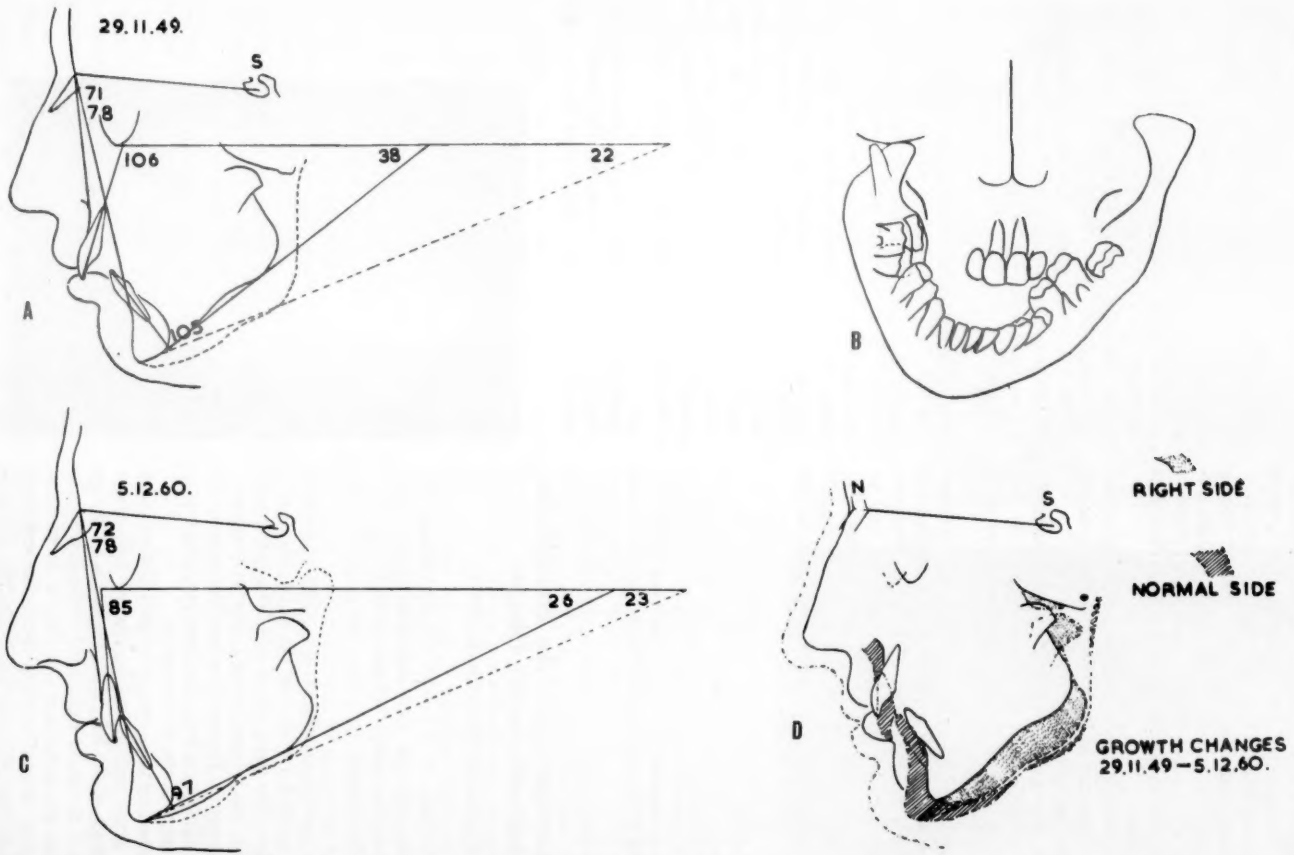


Fig 3 *Tracing of radiographs. Lateral and postero-anterior skulls at 11 years 6 months* (A & B), *lateral skull at 22 years 7 months* (C) *and superimposed lateral skull tracings* (D)

growth this cannot be estimated with any certainty although the birth weight (unless premature), the family background and general serial growth records may be of help. It is important that serial standardized facial photographs, with the camera at least five feet away from the face to reduce distortion, serial cephalometric lateral and postero-anterior skull radiographs and serial study models be recorded.

(*d*) The possible effects and limitations of orthodontic treatment with particular reference to the soft tissue posture and activity.

In this case it was possible to help the patient by careful assessment of serial records and on this basis it was decided to adopt the second course.

Acknowledgments: I am indebted to Professor R V Bradlaw and Professor G E M Hallett for the early records of this patient, to Professor F E Hopper for details of treatment and to Professor G L Howe for help in preparing this report. I am also grateful to the Photographic Department of the Newcastle upon Tyne Dental Hospital for the illustrations.

REFERENCES

Charles S W (1925) *Brit. dent. J.* **50**, 621

Low A (1952) Growth of Children. Aberdeen

Rushton M (1944) *Brit. dent. J.* **76**, 57

Sarnat B G & Engel M B (1951) *Plast. reconstr. Surg.* **7**, 364

Walker D G (1957) *Dent. Practit.* **7**, 160

Multilocular Cyst of the Mandible in a Patient with Paget's Disease

by A J MacGregor BDS FDS RCS (*Leeds*)

Large tumours of the jaws are increasingly uncommon, and the one described has further interest in that it occurred in a mandible involved by Paget's disease.

Clinical findings: A 69-year-old widow presented with a painful swelling of the right side of her lower jaw. The pain, which had been present for one week, was relieved when a discharge occurred into her mouth. The swelling had been present for at least nine years, for it had been noted when her second set of dentures were made.

The swelling was most prominent in the region of the angle and ascending ramus, with slight prominence of the left molar region. A sinus was present in the lower right third molar region. On palpation the expansion was felt to be of bony consistency, extending from the molar region to the temporomandibular joint. Neither the submandibular nor the cervical lymph nodes were palpable. There was normal sensation in the lips.

Radiographic examination: The expanded mandible contained a multilocular cyst with cavities of different sizes and there was a soap-bubble appearance in the right premolar region. The lesion involved almost all the right side and crossed the mid-line to the left canine area. A cotton-wool appearance of the calvarium was noted and intra-oral views of the maxilla showed a faint ground-glass appearance (Fig 1). A skeletal survey demonstrated that Paget's disease was confined to the skull.

The differential white cell count, serum calcium, phophorus, and alkaline phosphatase were within the normal range. The Wassermann reaction was negative.

Biopsy: A wedge of tissue including some bone was removed from the cyst wall at the posterior margin of the opening. Histological examination showed the cavity lined with squamous epithelium. There was no evidence of adamatinoma. The bone, which was of the coarse woven variety, had internal reversal lines, and some of the islands had brush borders. The appearance was similar to that found in Paget's disease. Bone from the right maxillary third molar region showed the disease more clearly, internal markings were more numerous and there were abundant osteoclasts and some osteoblasts (Fig 2).

Treatment: The Paget's disease was asymptomatic and required no treatment. The cystic lesion presented diagnostic difficulties. Biopsy sup-

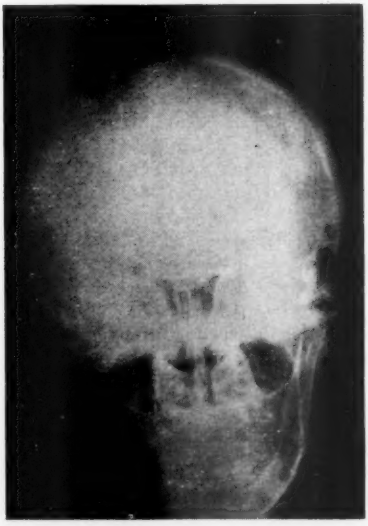


Fig 1 *Radiograph showing pagetoid lesions of calvarium and multilocular cyst of right mandible*

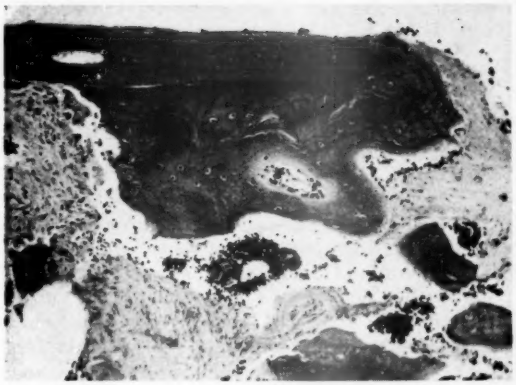


Fig 2 *Biopsy from maxilla showing mosaic appearance. H & E × 105*

ported the clinical impression that the main cavity was probably due to a cyst. It was not possible to get material from that part of the lesion which radiographically resembled adamantinoma. Difficulties in interpreting cystic appearances on radiographs are well known. Adamantinoma may simulate cyst but where the lesion is absolutely typical of adamantinoma there is a good reason to suppose it is present. It was thought, therefore, that the patient had a large cyst with an adamantinoma present in the wall – a well-recognized condition.

Very shortly after first being seen the sinus had enlarged and the cavity discharged its contents. There were no symptoms and the patient, being motivated by a terror of surgery, kept a high standard of hygiene. She did not wish to wear a denture, and when the purpose of an obturator was explained, her increased efforts at syringing the cavity proved the appliance to be unnecessary. Five months later the cavity was much smaller, the radiograph showing a great amount of bone production around the main cavity (Fig 3). There was complete obliteration of the internal markings and the appearance presented was that of a healing marsupialized cyst.

Comment: Treatment of adamantinoma has been reviewed by Battle & Winstock (1961). Surgery is favoured, such as resection of the mandible bearing the tumour with plastic restoration, or resection of the tumour with an attempt to maintain continuity of the lower border. Parker (Levy *et al.* 1955) says that as long as the area housing the tumour is kept open after curettage there is no recurrence. Radiotherapy has been found disappointing. Grant (Levy *et al.* 1955) has pointed out that the curative level of dosage is too near that known to cause osteoradionecrosis. All these procedures are formidable.

Fig 3 *Radiograph showing appearance five months after first visit*

Because of her attitude to surgery under local anæsthesia, and her unsuitability for general anæsthesia owing to bronchitis, this patient has virtually treated herself. Her progress was so rapid that the entire cavity is now thought to have been due to a cyst. The cyst itself was very unusual in that it so closely simulated adamantinoma radiographically.

In dealing with any cyst the possibility of adamantinoma should be borne in mind. This report suggests that observation after marsupialization is a valuable aid to diagnosis when a determined effort at biopsy would cause the patient great discomfort. The influence of the Paget's disease on the development and regression of the cyst is impossible to assess, but it is felt that the production of bone after natural marsupialization was unusually rapid for a woman of her age.

Acknowledgments: I am indebted to Professor F E Hopper for his help and advice, to Mr P Hart for the histology and to Mr L Jepson for the photographs.

REFERENCES
Battle R J V & Winstock D (1961) *Brit. J. plast. Surg.* **13**, 349
Levy B M, Parker D B & Grant R N (1955) *Oral Surg.* **8**, 682

Books recently presented and placed in the Society's library

(*Continued from p. 442*)

Centre International de l'Enfance
Calendrier des vaccinations. Séminaire organisé par le Centre International de l'Enfance sous la présidence du Professeur Robert Debré. Chateau de Longchamp, 19–21 Octobre 1959
pp 344
Paris: Masson 1960

Luis Dao L
Experiences sobre enfermedades tropicales en zonas rurales de Venezuela
pp 393
Caracas: Corporation Universo Ltda 1960

Lupu N Gh et al
Sclerozele pulmonare
pp 373
Bucuresti: Academiei Republicii Populare Romine 1960

McConnel J K
The adjustment of muscular habits
pp 129 4s 6d
London: Lewis 1933

Macdonald W W
Malaysian parasites XXXV–XLIX
pp 249 21s
Kuala Lumpur: Institute for Medical Research 1960

Mandahl-Barth G
Intermediate hosts of schistosoma: African Biomphalaria and Bulinus
pp 132 20s
Geneva: World Health Organization 1958

Medical Research Council
The hazards to man of nuclear and allied radiations Sir Harold Himsworth, Chairman
2nd report Cmnd. 1225
pp 154 7s
London: HMSO 1960

Mendez C
Book of bodily exercise. Translated by Franisco Guerra
Edited by Frederick G Kilgour
pp 122 $10
New Haven Conn.: Elizabeth Licht 1960

Metchinikoff E
Lectures on the comparative pathology of inflammation: delivered at the Pasteur Institute in 1891. Translated from the French by F A Starling and E H Starling
pp 218
London: Kegan Paul, Trench and Trubner 1893

Morris J R
Employment opportunities in later years
pp 125 $2.50
Burlingame, Calif: Foundation of Voluntary Welfare

Orenstein A J ed
Proceedings of the pneumoconiosis conference held at the University of Witwatersrand, Johannesburg, 9th–24th February, 1959 (Convened by the South African Council for Scientific and Industrial Research)
pp 632 £6
London: Churchill 1960

Owen E B
Cleft-palate and hare-lip: the earlier operation on the palate
pp 111
London: Baillière 1904

Pardo-Castello V
Diseases of the nails
3rd ed pp 284 68s
Springfield, Ill: Thomas 1960

Petrik M
The training of sanitary engineers: schools and programmes in Europe and in the United States
pp 151 20s
Geneva: World Health Organization 1956

Pharmacopoeia Internationalis
International pharmacopoeia. Supplement: recommended specifications
pp 224
Geneva: World Health Organization 1959

Pollitzer R
Cholera
pp 1019 £5
Geneva: World Health Organization 1959

Section of Proctology

President R W Nevin TD FRCS

Meeting January 25 1961

Cases and Specimens

Lymphosarcoma of the Rectum
Ian P Todd MS

Mrs E J, aged 21, housewife.

History: July 1960 rectal bleeding. Three weeks later biopsy of rectal tumour in Winnipeg General Hospital. Diagnosis lymphosarcoma. She was given a course of cobalt therapy as an out-patient, daily for five weeks, receiving 4,500 r from the anterior and posterior fields. There was an initial response but by late September the lump had increased in size and was bleeding. There has been no normal menstral period since the radiotherapy.

On examination: On rectal examination, an ulcer approximately 1·5 in. in diameter, situated posteriorly just above the anorectal ring, could be felt; it was mobile. The vagina appeared free of involvement. No other abnormality was found

Investigations: Biopsy (18.10.60) of rectal mucosa and submucosa: The submucosa is extensively infiltrated by lymphosarcoma. Many of the cells are necrotic and appearances suggest a higher degree of invasiveness compared with the previous biopsies. Chest X-ray at this time showed an opacity in the region of the third left rib. Tomography suggested an epipleural lesion; this had not been present three months previously. Iliac marrow puncture normal. Hæmoglobin 76%.

Operation: (25.10.60): *Synchronous combined abdominoperineal excision of rectum* (Mr Ian Todd and Mr Naunton Morgan). Abdominal viscera normal, liver clear. Enlarged, soft glands felt in mesentery of ileum. Posterior vaginal wall excised. Inferior mesenteric artery tied at its origin.

Progress: Good recovery. Chest X-rays: 23.11.60: The opacity previously seen in the left side of the chest has almost completely disappeared. 16.12.60: No lesion seen.

Morbid anatomy: Appearances: Lower sigmoid colon, rectum and anal canal 15·5 in. in length, together with a portion of the posterior vaginal wall. A protuberant growth 1·5 in. in diameter is situated on the posterior and right lateral quadrants of the lower third of the rectum. Its margins are covered by intact mucosa but the centre is occupied by a sloughing ulcer. There are 12·5 in. of bowel above the growth. In the neighbourhood of the tumour the mucosa shows fine petechial hæmorrhages (Fig 1).

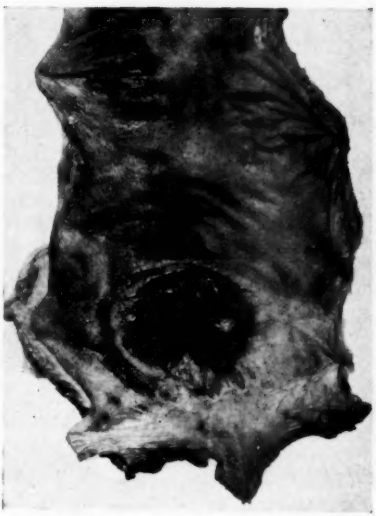


Fig 1 *Lymphosarcoma of rectum (close-up)*

Histology: The tumour is a lymphosarcoma of the large cell type.

Spread: Local – there is spread into the perirectal tissues to a slight degree. Lymphatic – no metastases present in 13 hæmorrhoidal glands examined. Venous – no evidence found.

Classification: Lymphosarcoma of rectum. Slight local spread. No lymphatic metastases.

The following points were brought out in the discussion: (1) Lymphosarcoma of the rectum is a rare disease but of a solitary nature, whereas lymphosarcoma of the small intestine is often a diffuse disease. (2) Surgical treatment carries a much better prognosis than deep X-ray therapy. (3) The survival rate is possibly as good as that of carcinoma of the rectum, though the figures available are small. (4) Radical extirpation of the disease is therefore justified.

Carcinoma of the Rectum Following Ileoproctostomy and Colectomy for Ulcerative Colitis

C N Hudson FRCS (for Ian P Todd MS)

Considerable differences of opinion exist on the surgical treatment of ulcerative colitis. The occurrence of a carcinoma in the retained rectum after ileoproctostomy is a theoretical possibility. Such a case is now recorded showing many of the features of malignant change in ulcerative colitis.

Case report (reported by Corbett 1953)
Mr R D, born April 1929

History: 1943: Aged 14. Onset of diarrhœa with blood and mucus. He was also suspected of having pulmonary tuberculosis, but this diagnosis was not sustained after investigation.

1946: Aged 16. Weight 3 st 10 lb. Ten stools a day. 25.1.46: Ileostomy and appendicectomy. 23.8.46: Readmitted with acute osteomyelitis of the right radius. 12.9.46: Drainage of bone abscess. 30.11.46: Readmitted with osteomyelitis affecting all four limbs. Treated with penicillin and immobilization in plaster.

4.3.47: Readmitted; pyoderma of left leg. 25.3.47: Subtotal colectomy. The rectosigmoid stump was retained. Report (Dr C E Dukes) shows typical severe chronic ulcerative colitis. No evidence of tuberculosis (Fig 1).

25.5.49: Aged 19. Readmitted for ileoproctostomy. The rectum was discharging once a month. 3.6.49: Establishment of mid-line ileostomy. 28.6.49: Amputation of ileostomy and insertion of enterotome. 12.7.49: Extraperitoneal closure of ileostomy.

5.5.50: Bowel actions three to four times daily. Gaining weight. Very satisfied with operation, but did not keep subsequent appointments.

Since last visit the patient lost no days of work through illness until current upset. His bowel action was semi-solid, usually three times a day. He ran his own business as a decorator, married and had 3 children.

July 1960: Sudden onset of central abdominal pain followed by profuse watery diarrhœa. This subsided after one month of treatment from patient's practitioner. Constipation and considerable tenesmus. The diarrhœa returned whenever the medicine was not taken. Acute loss of weight.

30.9.60: Referred to hospital with a diagnosis of recurrent ulcerative colitis. A carcinoma of the rectum could be felt with the finger tip and biopsy showed a poorly differentiated adenocarcinoma.

18.10.60: Combined abdominoperineal excision of rectum, with terminal ileostomy (Mr Ian Todd).

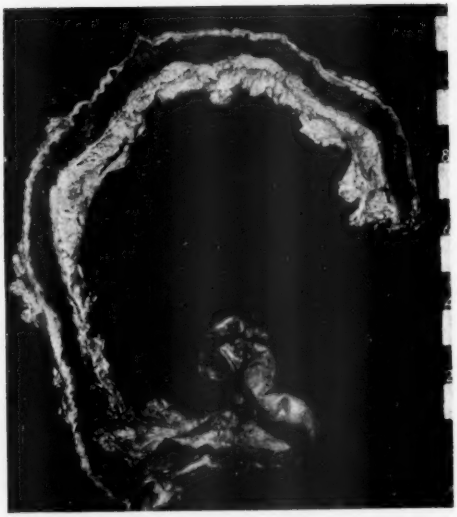


Fig 1 *1947. Colectomy Specimen. Ulcerative colitis*

28.11.60: When last seen he had put on 14 lb in weight and was back at work.

Pathology: The specimen (Fig 2) consists of about a foot of small intestine, an ileorectal anastomosis and the rectum and anal canal 8 in. in length

Two inches below the anastomosis an ulcerating growth 2 in. in diameter, almost encircles the upper third of the rectum.

The tumour is a very anaplastic carcinoma showing some areas of mucus-secreting signet-ring cells. The growth is of high grade malignancy. Sections through the rectal mucosa present the appearances of quiescent ulcerative colitis.

Spread: Local – slight invasion of perirectal fat. Lymphatic – metastases present in three of thirty hæmorrhoidal lymph nodes examined. The enlarged nodes in the mesentery of the small intestine are free from growth. Venous – invasion of the submucous and extramural veins (Fig 3).

Classification: Anaplastic mucus-secreting signet-ring cell carcinoma of the rectum. High grade malignancy associated with quiescent ulcerative colitis. 'C.1' (Dukes).

Discussion

Malignant change is now widely accepted as a complication of ulcerative colitis. Few surgeons would regard the risk of carcinoma alone as an indication for surgery, but it is undoubtedly a factor to be entertained in deciding treatment.

Fig 2 *1960. Carcinoma of rectum and ileorectal anastomosis. Quiescent ulcerative colitis*

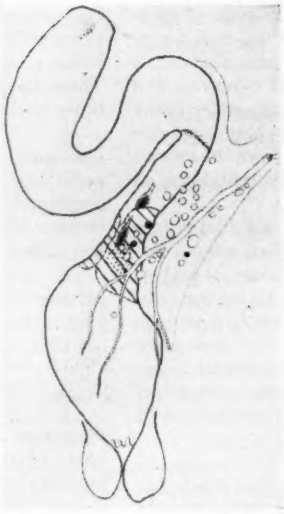


Fig 3 *Diagram of rectum and ileorectal anastomtosis showing position of growth and involvement of lymphnodes (1960)*

Colectomy is now performed more readily than heretofore. The vexed question concerns the management of the rectum. This may be retained for immediate or deferred ileoproctostomy. If continuity is not to be restored, most surgeons will perform abdominoperineal excision.

Mayo *et al.* (1956) reviewed the natural history of the rectal stump in 45 out of 241 cases of subtotal colectomy in which it was retained for more than three months. There was a high incidence of disease, including 2 cases of carcinoma in the rectal stump. Goldgraber *et al.* (1958) also report 2 cases of carcinoma in the rectal stump after subtotal colectomy.

Dawson & Pryse-Davies (1959), in reviewing carcinoma in ulcerative colitis, mention 2 cases following subtotal colectomy. One of these occurred in the rectal stump after ileorectal anastomosis. Aylett (1960) referring to this case suggested that the carcinoma may have been present, but unrecognized, at the time of operation.

Slaney & Brooke (1959) in 304 recorded cases of carcinoma in ulcerative coltis found 11 cases after subtotal colectomy. Of these, 3 patients had undergone ileoproctostomy. One of these patients (Cattell & Boehme 1947) developed carcinoma of the rectum after subtotal colectomy and ileoproctostomy for ulcerative colitis complicated by two separate primary carcinomata of the colon. The other 2 were reported by Dennis & Karlson (1952). One followed biopsies of suspicious polyps in the rectum on two previous follow-up visits; the other had failed to attend for follow-up for four years after ileorectal anastomosis. Dragstedt (1959) also reports a fatal case, but no clinical details are given.

It is possible that 3 of these cases had a neoplastic process already present at the time of ileorectal anatomosis. The case described here is not qualified in this way. Moreover it has many of the features which have come to be associated with cancer in ulcerative colitis. The cancer arose in a young man at least ten years before the age group commonly expected. It arose in a patient who suffered from ulcerative colitis for more than ten years, in whom the colitis began before the age of 16, this offering an extra risk of subsequent malignant change (Jackman *et al.* 1940). Finally it has appeared during the quiescent phase of the disease and is of high grade malignancy.

Certain other points need to be emphasized. The patient was virtually symptom free for nearly ten years. Nevertheless the rectum had not returned to normal after excision of the rest of the large bowel. The mucous membrane was healed, but not normal, and this quiescent phase seems to be the most dangerous time for malignant change (Dawson & Pryse-Davies 1959).

Three months delay occurred before the patient returned to hospital, because both he and his medical attendant attributed his symptoms to a recurrence of colitis. This delay in diagnosis is not uncommon in ulcerative colitis cases, because the clinical picture is so confusing. It is well known that similar difficulty occurs in radiological diagnosis of lesions higher up the colon, but such difficulty may also arise in making an early diagnosis of cancer in the rectum through a sigmoidoscope. One of the features of cancer, complicating ulcerative colitis, is that it may arise and spread in the submucous plane long before ulceration and typical appearances occur.

The patient described was lost to follow-up for ten years, and it is becoming increasingly obvious that all cases of ulcerative colitis of long standing in which any portion of the diseased bowel is retained must be closely followed up. The question is also raised whether routine mucosal biopsies at regular intervals should be obtained from the

retained rectum in view of the difficulty of spotting early malignant change by the naked eye. Indeed, histological evidence of persistent colitis has been found in patients without symptoms and with normal sigmoidoscopic appearances (Dick & Grayson 1961). Exfoliative cytology is liable to be confusing because the cells from the rectum in ulcerative colitis tend to be bizarre (Boddington & Truelove 1956).

Ulcerative colitis in childhood and adolescence has such a sinister reputation (Watkinson 1961) that colectomy may have to be advised. It may be that proctocolectomy will prove to be the right operation for these cases with a special risk. The rectum is the commonest site for malignant change in ulcerative colitis, and subtotal colectomy has been shown to be no protection against this complication. Moreover proctocolectomy is the only certain cure of the colitis.

Acknowledgments: I would like to thank Mr Rupert Corbett and Mr Ian Todd for permission to report this case and Dr Cuthbert Dukes, Dr R J Cureton and Dr B C Morson for the pathological reports. The Photographic Departments of St Bartholomew's Hospital and St Mark's Hospital produced the illustrations.

REFERENCES
Aylett S O (1960) *Ann. R. Coll. Surg. Engl.* **26**, 260
Boddington M M & Truelove S C (1956) *Brit. med. J.*, i, 1318
Cattell R B & Boehme E J (1947) *Gastroenterology* **8**, 695
Corbett R S (1953) *Proc. R. Soc. Med.* **46**, 1028
Dawson I M P & Pryse-Davies J (1959) *Brit. J. Surg.* **47**, 113
Dennis C & Karlson K E (1952) *Surgery* **32**, 892
Dick A P & Grayson M J (1961) *Brit. med. J.* i, 160
Dragstedt L R (1959) In: Disturbances in Gastro-Intestinal Motility. Ed. J A Rider & H C Moeller, Oxford; p 256
Goldgraber M B, Humphreys E M, Kirsner J B & Palmer W L (1958) *Gastroenterology* **34**, 809
Jackman J, Bargen J A & Helmoltz H F (1940) *Amer. J. Dis. Child.* **59**, 459
Mayo C W, Fly O A & Connelly M E (1956) *Ann. Surg.* **144**, 753
Slaney G & Brooke B N (1959) *Lancet* ii, 694
Watkinson G (1961) *Brit. med. J.* i, 147

Right Hepatic Lobectomy for a Solitary Metastasis

M J Killingback FRCS
(for H E Lockhart-Mummery MCh FRCS)

W P, female, aged 61

History: In July 1958 a transverse colostomy was performed to relieve acute large bowel obstruction. In August 1958 a carcinoma of the sigmoid colon was resected by Mr W B Gabriel. This appeared to be a radical operation although there was a small nodule felt in the liver and a diagnosis of metastasis could not be excluded. The neoplasm was of low-grade malignancy, a 'B' case. There was permeation of a vein in the muscle wall of the bowel by carcinoma. The patient was well and symptom free for two years and five months.

On examination (November 1960): Routine examination revealed a large lump in the liver which appeared to be confined to the right lobe. There was no clinical or radiological evidence of other distant metastases.

Operation (November 1960): Laparotomy was performed and a solitary hepatic metastasis was confirmed. The incision was converted to a right thoraco-abdominal and right hepatic lobectomy was undertaken.

The post-operative recovery was delayed by persistent collapse of the right lung base associated with a small pleural effusion. An abscess in the right subphrenic space discharged along the abdominal drain wound until the patient left hospital four weeks after operation.

Pathology: The solitary metastasis in the right lobe of the liver measured 3 in. in diameter. Microscopically, this was an adenocarcinoma similar in histological structure to the primary tumour of the colon removed previously. Examination of two lymph nodes related to the neck of the gall-bladder showed similar metastatic adenocarcinoma in one. There was permeation of veins in the connective tissue around the gall-bladder.

Comment: This patient, with an isolated hepatic metastasis from a tumour of low-grade malignancy, appeared to be an ideal case for hepatectomy. The unusual spread around the gall-bladder, detected on histological examination of the hepatectomy specimen, must seriously affect the prognosis.

Chronic Ulcerative Colitis not Involving the Rectum. Carcinoma of Lower Third of Rectum. Rectovaginal Fistula

P T Savage FRCS

Mrs M R, aged 66.

History: One year ago, blood-stained vaginal discharge. Two months ago she had attacks of colicky abdominal pain, and passed fæces *per vaginam*. No previous history to suggest ulcerative colitis.

On examination: Thin, pale, wasted woman of 66. Tongue clean. C.V.S. and R.S. normal. Abdomen: No tenderness, no mass palpable, liver not enlarged. *Per rectum:* A hard non-tender mass occupied the lower third of the rectum. A finger could be passed through a large rectovaginal fistula. *Per vaginam:* Fistula was easily palpable. The growth involved only the posterior vaginal wall and the adjacent part of the cervix.

Fig 1 *Second-stage combined synchronous abdominoperineal posterior pelvic exenteration for carcinoma of lower third of rectum with a rectovaginal fistula. There is severe chronic ulcerative colitis involving the pelvic colon, which stops abruptly at the rectosigmoid*

Progress and Treatment

Operation 16.6.59 (Mr Savage): Examination under anæsthesia; several biopsy specimens taken. The abdomen was opened through a 6-inch lower mid-line incision. One small secondary carcinomatous nodule was found in the liver but no carcinomatosis peritonei. The growth involved the pouch of Douglas. A small perforation was present through into the vagina. The opening was closed by suturing the rectum to the cervix. The pelvic colon was divided and a defunctioning left inguinal colostomy carried out, the lower end being brought out through the incision, the upper end through an incision in the left iliac fossa. On dividing the colon the changes of ulcerative colitis were noted in the mucosa. Convalescence uneventful. Her anæmia (Hb 50%) was corrected by blood transfusion (3 pints).

Second operation: 8.7.59 (Mr Savage and Mr S Strange):

A combined synchronous abdominoperineal posterior pelvic exenteration was carried out, the pelvic colon, rectum, anus, uterus, adnexa and vagina were removed *en bloc*. A small piece of vaginal mucosa around the urethra was left behind. Fig 1 shows the resected specimen.

Histological report: Well-differentiated tubular columnar cell carcinoma of rectum.

Follow-up: She remained well and active for thirteen months. She then became jaundiced and died (at home) after an illness of four weeks. No post-mortem.

Multiple Primary Lymphosarcomas of the Large Intestine Complicating Chronic Ulcerative Colitis

J S Cornes MB DCP (for B C Morson DM)

Mrs M Z, aged 42, gave a fifteen-year history of chronic ulcerative colitis. The disease had been quiescent for four years, and had recurred only two months before her admission to St Mark's Hospital under the care of Mr O V Lloyd-Davies.

On examination: No palpable lymphadenopathy; W.B.C. within normal limits; chest X-ray normal.

A one-stage proctocolectomy with terminal ileostomy was performed: the liver, spleen and abdominal lymph nodes appeared normal.

Examination of the operation specimen showed a chronic ulcerative colitis, in the healing phase, affecting the whole colon and rectum. Two tumours were found: one encircling the sigmoid colon over a distance of 10 cm, and one in the upper third of the rectum approximately 5 cm in diameter. Both tumours infiltrated the muscle coats, and the upper tumour also infiltrated the pericolic fat. Histological examination of the sections from the two tumours showed lymphoblastic lymphosarcomas. Regional lymph nodes not involved. The pathological features have been described elsewhere (Cornes *et al.* 1961).

Six months after the operation the patient developed a large palpable mass in the left iliac fossa which was considered to be a recurrent tumour. Deep X-ray therapy was given, and no tumour has been palpable since. When last seen, one year after the operation, the patient was in good health.

This is the only case seen at St Mark's Hospital. We have been informed that no similar case has been seen at Birmingham University (Brooke 1959), the Gordon Hospital, London (Dawson 1961), or the Radcliffe Infirmary, Oxford (Truelove 1960).

Acknowledgment: We are grateful to Mr O V Lloyd-Davies for the clinical details of this case.

REFERENCES
Brooke B N (1959) Personal communication
Cornes J S, Smith J C & Southwood W F W (1961) *Brit. J. Surg.* (in press)
Dawson I M P (1961) Personal communication
Truelove S (1960) Personal communication

Paget's Disease of the Anal Canal

Hugh Guerrier FRCS and I W Whimster MB

In May 1954, a man of 68 years was referred to a dermatologist with a three-year history of pruritus ani. He was found to have patches of lichenification around the anus and was treated with local applications, amongst which crude coal tar figured prominently.

By October 1954 he was no better and then received superficial X-ray therapy. By June 1955 there was no improvement and a course of hydrocortisone ointment was given.

In September 1955 no improvement was present and a biopsy produced a histological report of extra-mammary Paget's disease and the whole lesion was excised locally in October 1955.

The excised specimen showed Paget cells within the epithelium of the whole lesion. In one area they were starting to invade the underlying connective tissue as an adenocarcinoma.

The patient was well for four years, during which time he was examined at monthly, three-monthly, and six-monthly intervals.

October 1959: Pruritus recurred. A small, superficially eroded reddened lesion was found at approximately the same site.

November 1959: A second biopsy showed a small focus of adenocarcinoma.

February 1960: Local excision: histology showed adenocarcinoma. Abdominoperineal excision of rectum: histology revealed Paget's disease and adenocarcinoma of the squamous epithelium of the anal canal, and secondary adenocarcinoma in two lymph nodes.

So far, twelve months later, there is no evidence of recurrence.

Primary Crohn's Disease of Rectum with Colo-vesical Fistula

C Patrick Sames MS FRCS

Male, aged 33, Civil Servant

March, 1959: Referred by consulting physician because of persistent diarrhœa, urinary frequency and dysuria and, of late, pneumaturia and passage of fæcal material in urine. The diarrhœa had been present more or less continuously for ten years, about 6 stools a day – yellowish and occasionally streaked with blood. Admitted on two occasions for investigation and treatment.

Past history: Operated on for fistula-in-ano, first at the age of 12 with apparent success, and again in 1951 when the wound took about six months to heal. Following the operation he had remission from diarrhœa for some months. The fistula was reported as being 'tuberculous' on account of 'typical giant cells'. (At this time he had a brother undergoing treatment for pulmonary tuberculosis.) No history of tropical diseases.

Examination revealed stenosis and rigidity of the anal canal. Perianal scarring on the right side, but no active ulceration or fistula formation. The sigmoidoscope revealed friable red granulations and could not be passed beyond 5 cm due to stenosis of rectum above. Abdominal examination revealed colon heavily laden with fæces. Barium enema confirmed these findings.

Diagnosis of 'segmental colitis' with colo-vesical fistula.

Laparotomy (14.3.59).
Findings: (1) Rigid stenosed lower sigmoid and rectum with attachment to posterior wall of bladder on left side. (2) High fixation of cæcum with thickening and rigidity of cæcum and ascending colon. Terminal ileum normal. (3) Skip lesion about 6 in. long in upper jejunum – red, œdematous, but not stenosed.
Procedure: (1) Standard abdominoperineal excision of rectum with closure of bladder fistula and formation of terminal iliac colostomy. (2) Standard right hemicolectomy. (3) No surgical interference with skip lesion of jejunum. Uninterrupted recovery; now in excellent health (twenty-two months later).

Pathology (*Dr R Bishton*)
(1) *Ascending and right transverse colon:* Gross: Terminal 8 cm of ileum, cæcum, appendix and 20 cm of colon. The appendix is thickened. The proximal ascending colon shows a 6-cm length of severe narrowing due to white fibrous thickening of the bowel wall; the overlying mucosa appeared to be ulcerated. Another similar segment is present 9 cm farther on.

The cæcum, ascending and transverse colon all show mucosal ulceration and a heavy submucosal infiltration by lymphocytes, plasma cells and eosinophils. The mucosa of the appendix is intact and there is no inflammatory exudate in the lumen. A lymph node in the appendicular region shows several foreign body giant cells containing birefringent material.
(2) *Anus, rectum and descending colon:* Gross: This segment measures 32 cm in length and shows extensive mucosal ulceration, mural thickening and narrowing.

The rectum shows similar changes to the colon but the inflammatory reaction extends in places into the circular muscle coat. Autonomic nerves and ganglia are large and prominent.

A striking feature of these sections is the predominantly submucosal inflammation with

an accompanying hypertrophy of the muscularis mucosæ. No tuberculoid follicles are present in the bowel wall.
Opinion: Ulcerative colitis.

Comment:
The histological differentiation of Crohn's disease and ulcerative colitis is notoriously difficult. In all humility, and with apologies to my pathologist colleague, I would like to suggest that on clinical grounds this case cannot be anything other than Crohn's disease, the major manifestation having arisen in the rectum with skip lesions in the right colon and jejunum. The earlier history of recurrent fistula-in-ano is also significant.

Basal Cell Carcinoma of Anal Canal
C Patrick Sames MS FRCS

Woman, aged 48
24.10.58: Referred to hospital because of rectal bleeding at end of bowel action.
On examination: A well-pedunculated tumour about 1·5 cm across was found just within the anal canal. Sigmoidoscopy to 20 cm revealed no other abnormality.

5.11.58: Excision of pedunculated tumour with generous amount of the base. Tumour very friable. *Histological report:* A pedunculated basal-cell carcinoma of anus. The base is clear of the tumour. (Sections were referred to Dr B C Morson, who confirmed the diagnosis but drew attention to the sinister prognosis and advised radical excision.)

24.11.58: Patient not anxious for more radical surgery, but in view of Dr Morson's report a further local excision was undertaken to check that the base was clear. *Histological report:* There are small pieces of rectal mucosa, fibrous tissue and granulation tissue. No evidence of basal cell carcinoma.

27.2.59: Local induration noted at site of previous excision. Biopsy showed some fibrosis in the submucous layer, with few nodules of basal cell carcinoma. The overlying mucosa was intact.

11.3.59: Abdominoperineal excision of rectum; terminal iliac colostomy. Liver normal to palpation.
Histology (Dr R Bishton): Gross: Anus, rectum and colon (overall length 22 cm). Just above anal margin there is an indurated small area which is slightly puckered but not obviously ulcerated. This shows intact ano-rectal mucosa with masses of underlying basal cell carcinoma some of which are cystic. These are infiltrating deep down through the muscle layers of the wall. Two small lymph nodes show reactive hyper-plasia and lymphœdema but they are not invaded by tumour.
Subsequent history: Quite well until June 1960. By 21.10.60 there was enormous nodular enlargment of liver, ascites and gross cachexia, perineal scar firm and satisfactory; no local recurrences.

Pseudoxanthoma Elasticum: Severe Melæna from the Jejunum Treated by Resection
C Patrick Sames MS FRCS

Man, aged 81. Admitted because of frequent passage of black stools for the preceding three days. No significant history; no abnormal physical findings apart from obvious anæmia. A tentative diagnosis of bleeding peptic ulcer was made. On admission the hæmoglobin was 48%. Despite slow transfusion of five pints of blood the rectal bleeding persisted with passage of clots and dark red blood and the diagnosis was revised to one of possible diverticulitis. With further blood transfusion the hæmoglobin was eventually raised to 70%, and the blood pressure to 100/50 and laparotomy undertaken.
Laparotomy (three days following admission): No diverticulitis; no peptic ulcer. Spleen and liver normal. The whole bowel was heavily loaded with blood up to about the upper third of the jejunum, at which point there appeared to be a sudden cessation of blood in the lumen, the bowel above being normal. A sigmoidoscope was passed into the jejunum, but no significant lesion could be detected. 18 in. of jejunum was resected (9 in. above and 9 in. below the point where it was judged that the bleeding was occurring). Continuity of the bowel was restored by end-to-end anastomosis. The man made an uninterupted recovery, and has remained well ever since.
Pathology: Normal-looking jejunum. Two random blocks showed normal histology.
During convalescence it was noticed that around the umbilicus there were a few isolated minute yellowish subcuticular papules. Nil elsewhere. Ophthalmoscopy revealed no angioid streaks. Biopsy of skin nodules showed very large amounts of degenerate and fragmented elastic fibres in the dermis. The elastic fibres did not stain black with elastic-trichrome stain, but appeared as red fern-like structures (resembling ice crystals on a window pane). The appearances were consistent with pseudoxanthoma elasticum.
Jejunum – supplementary histological report: In the light of the skin lesion a section of the intestine was stained for elastic tissue. All the arteries in the bowel wall showed that the normal thin internal elastic lamina is replaced by numerous thick rod-like fragments of elastic tissue, consistent with pseudoxanthoma elasticum.

Stenosing Colitis with the Formation of a Gastrocolic Fistula

J H O Earle MD and C Naunton Morgan MS

Married woman, aged 23; no children.

April 1957: Developed diarrhœa, the bowels opened four or five times a day. Stools loose with mucus but no blood. The symptoms were never severe and did not incapacitate her unduly. They gradually subsided but her stool never returned to normal and her bowels were open twice a day.

Shortly after the onset of diarrhœa she developed a painful red swollen knee-joint for about two weeks before it became normal again. She has since had many attacks of pain and swelling of the knees and ankles. 1958: Fissure-in-ano.

26.1.60–12.2.60: Admitted to the Royal Masonic Hospital. Since the onset of her illness she has had intermittent attacks of diarrhœa which she related to eating certain foods, particularly nuts. Latterly she noticed she was passing blood *per rectum*. The attacks of 'arthritis' continued.

Investigations: Barium enemas at Newcastle in 1957 and at the Royal Masonic Hospital in January 1960 showed two areas of narrowing, one in the transverse and the other in the descending colon. Radiologically the probable diagnosis was Crohn's disease rather than ulcerative colitis. The small bowel was normal. In January 1960 a small amount of barium was seen in the stomach and the possibility of gastrocolic fistula was raised. However, a barium meal in February failed to demonstrate a fistula. Other investigations were normal apart from a slight anæmia (Hb 78%, 11·5 g%), a raised E.S.R. (30–50 mm in 1h, Westergren) and an increased gamma globulin as shown on paper electrophoresis.

September 1960: Barium enema showed a gastrocolic fistula. November 1960: Barium enema after readmission confirmed the fistula and showed considerably more narrowing of the lesions of the colon.

Treatment: In 1957 in Newcastle she had been treated with rectal cortisone for three weeks without improvement. In January 1960 at the Royal Masonic Hospital she was seen by Dr T Hunt who considered that medical treatment should be given a further trial as her general health was good and she was relatively symptom free. She was put on Salazopyrin, one tab. b.d., and seen at regular intervals.

When the presence of the gastrocolic fistula was confirmed in September and also because she was anxious to start a family, it was decided to proceed with a total colectomy. This was performed on December 2 with closure of the gastrocolic fistula. She made an uninterrupted recovery and was discharged on December 22.

Operation specimen: Macroscopy: It consisted of the lower end of the ileum, cæcum, ascending, transverse and descending colon. The appendix was 6·0 cm long with a maximum diameter of 0·3 cm. It appeared to have undergone a change of obliterative appendicitis. In the ascending colon were two polyps. In the transverse and descending colon were two stenosing lesions, that in the transverse colon was 8·0 cm in length and at about the mid point of it was a fistula connecting the narrowed colon to the small portion of the stomach which had been removed with the colon. The fistula passed a fine probe without difficulty. The mucosa on the proximal side of the lesion showed ulceration extending over a longitudinal diameter of some 4·0 cm and almost completely encircling the bowel wall.

The second stenosing lesion, 8·0 cm from the first and similar to it was 16·0 cm long. The mucosa was ulcerated at both ends. The mucosal surface of the unstenosed ascending colon had a smooth shiny appearance such as is seen in the atrophic changes following ulcerative colitis, and the mucosa between the two areas of stenosis was similar.

Microscopy: The stenosed lesions show severe active ulceration of the mucosa with islands of intact mucosa remaining. The ulceration appears as vascular granulation tissue with infiltration by plasma cells, histiocytes and polymorphonuclear cells. The mucosa in the ascending colon and between the two stenosing lesions is thinned and the number of acini diminished. At the margin of the first stenosing lesion a crypt abscess was found. The polyp examined appears to be an inflammatory tag of mucosa.

In the submucosa, muscularis and serosa there is follicular lymphoid hyperplasia as well as more generalized lymphocyte infiltration which in some areas has the appearance of 'streaming' through the muscularis. The circular layer of muscle appears hyperplastic. One multinucleate giant cell (6 nuclei) of the foreign body type has been found but there are no giant cell systems present.

The mesenteric lymph nodes show reactive hyperplasia. The lower end of the resection is through normal bowel.

The histological changes in the appendix are those of obliterative appendicitis.

This case is presented because of the formation of the gastrocolic fistula and because clinically and radiologically the probable diagnosis was Crohn's disease whilst histologically the changes in the colon showed features which could be associated with this or with ulcerative colitis and were not conclusive of either.

[*Meeting to be continued*]

Book reviews

Sequential Medical Trials
by P Armitage MA PhD
pp 105 illustrated 20s
Oxford: Blackwell Scientific Publications Ltd 1960
Dr Armitage is the chief exponent in this country of the use of sequential analysis in clinical trials and it is convenient to have his views and original work on the subject in one book. Taking as his starting point the 'classical' controlled trial, Dr Armitage points out that for reasons of ethics and economy it may be desirable to ensure that a trial is not continued any longer than is necessary to produce a 'significant' result. In the classical trial a test of significance is, generally speaking, only valid if the size of the trial is predetermined. The sequential method provides, as it were, a running test of significance which can be applied as the results come in and therefore allows the trial to be stopped when the desired level of significance is reached. Dr Armitage describes the charts which he and others have devised for this purpose and also discusses the underlying principles.

The bulk of the book applies to trials based on qualitative criteria of assessment, such as simple preferences between two methods of treatment. Sometimes it is important to use a qualitative assessment, to take account of how much better one treatment is than the other in each individual case. Dr Armitage describes the sequential t-test which was developed for this purpose some years ago but has so far not been used much in the medical field.

This is not a cookery book. The clinician undertaking an occasional clinical trial merely to oblige a drug firm will not find here an easy recipe for his purpose. On the other hand it must certainly be read by anyone, statistician or no, wanting to know what sequential analysis really is and what possibilities it offers the worker.

Structure and Function of the Cerebral Cortex
edited by D B Tower & J P Schade
pp xi+448 illustrated 85s
Amsterdam &c: Elsevier Publishing Company
London: D Van Nostrand Company Ltd 1960
This volume contains the papers (with discussions) presented at the Second International Meeting of Neurobiologists, held in Amsterdam in 1959. Some 90 scientists from 15 countries participated in the three symposia dealing with anatomical (19 papers), physiological (12 papers) and biochemical (10 papers) aspects of the cerebral cortex. Each symposium is introduced and summarized by an authority in the field (Neuroanatomy – S T Bok and J Z Young; Neurophysiology – F Bremer and G Moruzzi; Neurochemistry – H Waelsch and D B Tower).

As is usual with such publications the contents are varied in type. No attempt is made to survey established knowledge regarding the cerebral cortex; the emphasis is entirely on recent researches and unsolved problems. This book will therefore be of use mainly to the research student and research worker interested in neurology. So specialized is work in this field that only a small proportion of the reports will be fully comprehensible to any one individual. However, to any interested in surveying the broad research trend this volume will be invaluable since the authors are of world-wide repute, and since it represents the thoughts, perplexities and controversies current in this branch of brain research.

The book is exceptionally well produced. The binding, paper, printing and reproductions are all excellent.

The Adrenal Circulation
by R G Harrison MA DM and M J Hoey BSc
pp vii+77 illustrated 25s
Oxford: Blackwell Scientific Publications Ltd 1960
For several years now, Professor Harrison has been interested in circulatory problems from both the functional and morphological point of view and in recent years has turned his attention to the adrenal gland. Much of his earlier work on the adrenal circulation has appeared in the *Journal of Anatomy* and elsewhere, but is brought together in this monograph along with several new observations some of which formed the subject of a BSc thesis by the junior author, Miss Hoey.

After describing the morphology of the adrenal circulation in man and the common laboratory animals the main thesis of this work is presented, that adrenal cortical activity is dependent to a large extent upon the degree of vascularization of the cortex. This is substantiated by experimental evidence to the effect that the injection of various pharmacological agents (adrenaline, histamine, serotonin, ACTH and several other substances) or noxious and 'stressful' stimuli (electrical stimulation of whole nerves, extremes of heat and cold and chemically induced tumours) can profoundly affect the vascularity of the adrenal cortex, either by a direct vasoconstriction of the medullary arteries or reflexly through the hypothalamus and the secretion of ACTH.

No reader of the monograph is likely to question the validity of this hypothesis or the evidence in its support, but many will question the value of a short monograph of this kind. Since it consists

almost entirely of experimental observations based on a single technique, the intra-arterial injection of a radio-opaque material, the new findings could well have been published as a paper or a series of papers in a scientific journal.

A Synopsis of Public Health and Social Medicine
by A J Essex-Cater MRCS LRCP DCH DIH FRAI
pp xii+563 55s
Bristol: John Wright & Sons Ltd 1960

Public health and social medicine cover a large field and this synopsis certainly contains an astonishing amount of factual information on a large variety of subjects. Sections on medical statistics, epidemiology, occupational medicine and toxicology, the various health and social services, international health and history of public health are all included. The index is well constructed but there are regrettably few references to more authoritative works and those cited seem rather arbitrarily chosen. No one person could be expected to have complete knowledge of so many subjects and inevitably there are errors of fact and emphasis. Those apparent to the reviewer were not particularly serious from the point of view of a student revising for an examination, but it is doubtful whether the book is sufficiently reliable as a work of reference for those faced with a problem affecting the public health; indeed the reader is warned by the author against this.

The Synopsis Series is well known to most medical readers and this volume, which is similar in appearance and layout to others, shares their merits and limitations. It is too detailed and indigestible for the undergraduate, but the post-graduate student of public health who finds a synopsis useful for revision and for organizing his thoughts will not be disappointed.

The Electrical Activity of the Nervous System
by Mary A B Brazier BSC PHD
2nd ed pp xiv+273 illustrated 35s
London: Pitman Medical Publishing Co Ltd 1960

The first third of this book deals with conduction in peripheral nerves. Then follow chapters on the synapse and neuromuscular junction, and on electrical events in the spinal cord and the various sense organs. The last third is devoted to the brain, including the electroencephalogram. Little of the book would be intelligible to anyone who did not already possess at least an ordinary medical student's knowledge of the physiology of the nervous system. It is essentially a supplementary text. The principal failing of the book is that the author does not have the gift of explaining complicated phenomena logically and clearly. Blunders, indeed, are not infrequent, and the approach is almost wholly uncritical. To offset this it has several merits. The author is good on history; she knows what the important advances have been and puts them in. The lists of references at the ends of the chapters are excellent. As a textbook for second-class honours candidates it will no doubt serve, but it is much to be hoped that first-class minds will not be introduced to the experiments of the great modern masters of neurophysiology through this unperceptive account.

Tablet and Capsule Identification Guide
pp 8 illustrated
Brochures 8s 6d
Set of 8 cards 17s 6d
London: Morgan Brothers (Publishers) Ltd (for The Chemist and Druggist) 1960

This booklet comprises photographs of 915 tablets and capsules, most of them coloured. Only those drugs are omitted which are labelled with their name (excellent practice) or look the same as another substance so that the two cannot be distinguished photographically.

The idea is excellent and the pictures are very helpful. But in many cases the differences between tablets are very slight indeed.

Toward the Diagnosis of Congenital Heart Disease
by W Carleton Whiteside
MD FRCS(C) FACS FICS DABTS
pp xi+86 36s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

Dr Carleton Whiteside's publication falls between two stools; it does not set out to be a textbook on cardiology, nor is it a synopsis, 'digest', or 'aid' from which help can easily be gained by a doctor in diagnostic difficulties. The author, in his own words, has attempted to collect a bouquet of other men's flowers, but they are rather an ill-assorted bunch, very loosely bound together.

Before proceeding to a general classification of individual congenital lesions, a considerable section is devoted to 'some general diagnostic principles'. Here are well over a hundred short unconnected statements on various aspects of heart disease set out in no sort of order. They will be difficult to remember and there is no means of reference to any particular point where information is sought. A short section follows on clinical diagnosis of congenital and acquired heart disease in children and on fœtal anoxia. Here information is incomplete, much is omitted and conditions almost unknown in childhood are included.

The main part of the book describes individual congenital lesions and their clinical features. This contains useful information and is more suitable for rapid reference, though the constant use of abbreviated lettering is disturbing, despite the key at the beginning.

The intention of the author is obviously to

simplify a complicated subject in medicine, but his method of writing short synoptic notes does not achieve this object and the reader is left in some confusion.

The Control of Disease in the Tropics
by T H Davey and W P H Lightbody
2nd ed pp xii+422 illustrated £2 7s 6d
London: H K Lewis & Co Ltd 1961

This book is not only an excellent teaching manual, but invaluable for quick reference by field-workers in tropical medicine. The welcome appearance of a second edition after six years indicates both the high reputation established by the first edition and the rapid growth of knowledge in this field. The method of presentation remains unchanged, but the work has been revised throughout, and there are new chapters on health education and poliomyelitis. There is an adequate index but, regrettably, no reference list for further reading.

Of outstanding value is the attention given to the economic effects, both immediate and remote, of particular developments in public health. The first chapter especially, with its excellent review of the socio-economic factors underlying good health, deserves a wider readership than a purely medical one, since it is concerned with policy-making in the widest sense.

While recognizing that health education is even more essential in backward than in advanced communities, the authors are wise to stress that a deep understanding of existing traditions must inform any new development.

The new drugs for such diseases as leprosy and tuberculosis are shown to facilitate control by methods which, unlike those of former days, do not altogether disrupt community life. As the authors point out, it is fortunate that immunizing processes are available to counteract poliomyelitis which, in an improved sanitary situation, tends to change its behaviour for the worse.

The treatment of problems of rural sanitation is on admirably simple and practical lines.

Clinical Child Psychiatry
by Kenneth Soddy MD DPM
pp x+470 42s
London: Baillière, Tindall and Cox 1960

In the preface to his new book, Dr Kenneth Soddy states that he thinks that child psychiatry needs detailed clinical observations of emotional illness, similar to those made on behalf of medicine by Sydenham and his contemporaries in the eighteenth century. He thinks that this needs to be done in order to build up a body of material from which to establish a classification of illness. No one practising child psychiatry would disagree with this statement, although the reviewer would consider that we are now well on the way to establishing certain clearly defined clinical entities.

It is with surprise then that one finds that Dr Soddy confines himself in his book much more to the normal than to the abnormal. The detailed description of the psychological state of the normal infant, older child and adolescent during their different stages of development, and what can go wrong at each stage, is very well described and extremely valuable. If the aim of this book, however, is to educate postgraduates in child psychiatry, one would have expected the clinical issues to have received more attention. There is scanty description or no account at all of the commoner psychosomatic disorders, the group of neurotic learning disturbances, obsessional illnesses and phobic illnesses, although these illnesses are amongst the commonest group of disorders encountered in clinical practice. In addition one looks in vain for reference to research studies and finds that there are only 20 references in the whole book.

The author has made his greatest contribution in attempting a new method of classification, and in showing the interaction of the child at each particular stage of development with the family members and how this interaction can lead to healthy growth or unhealthy deviations.

Respiration. Physiologic Principles and Their Clinical Applications
by P H Rossier, A A Bühlmann & K Wiesinger
edited and translated from the German Edition
by Peter C Luchsinger MD & Kenneth M Moser MD
pp 505 illustrated 118s
St Louis: The C V Mosby Company
London: Henry Kimpton 1960

This book is the first fairly comprehensive volume in English which deals with the physiology of respiration and its clinical applications and which contains all the latest advances in knowledge in this wide field. This subject has become increasingly complex and important during the last twenty years with the advances of cardiac and lung surgery and the understanding of anæsthetic and medical problems.

The book was first published in German in 1955 and has been translated, revised and brought up to date by Luchsinger and Moser who are supremely well qualified for this task. It is lucidly written in good English, the first part on normal respiratory physiology containing also chapters on tissue respiration, cyanosis and dyspnœa. The second part concerns the methods of investigating pulmonary function including cardiac catheterization and blood and alveolar gas analyses. The third part classifies the causes and types of respiratory dysfunction showing how recent advances

in the techniques of investigation have made these comparable. It includes vascular shunts and diffusion abnormalities. The fourth and longest part of this informative volume concerns clinical practice and provides a much needed help and stimulus to the practical physician dealing with all forms of respiratory dysfunction. Artificial respiration, high altitude breathing and pulmonary function in the athlete provide the final chapters which are followed by an appendix of useful information, equations and tables. There is a comprehensive and up-to-date bibliography of eighty pages.

The book has one drawback – it is too expensive and is, therefore, unlikely to find its way into the bookcases of the many physicians and surgeons who would find it informative, stimulating and very helpful.

Physiology in Industry
by Lucien Brouha MD DSC
Volume 4 of Modern Trends in Physiological Sciences
International Series of Monographs on Pure and Applied Biology
pp xii+145 illustrated 40s
Oxford &c: Pergamon Press 1960
The sub-title of this book 'Evaluation of industrial stresses by the physiological reactions of the worker' very reasonably indicates the intentions of Dr Brouha. This is not a textbook on industrial physiology (a textbook which is urgently required), but might be said to be an important part of a potential textbook.

Dr Brouha has drawn very largely on his own researches as an industrial physiologist in Canada and the United States. He deals systematically with the physiology of muscular work, and the modifications imposed by changes in environmental temperature. A final section of the book is concerned with the ways in which a physiologist evaluates industrial work, and can tackle the problem of reducing fatigue.

The application of physiology to industrial problems is only now beginning to develop, although there has been a very long period of pioneering. There is only one department of applied physiology in this country; the clinical aspects of human physiology have hitherto been dominant.

All those who are interested in a wider aspect realize the importance of the industrial field. Gradually, the industrialist (trade unionist and employer) has begun to appreciate that biologists have a part to play and a part which quite certainly is going to become more important in the future. Industrial medicine had considerable difficulties to start with, not least being the lack of books. The first attempts to write books in new fields are inevitably not going to be perfect, so Dr Brouha should be congratulated not only for writing a valuable book but for his pioneering spirit.

Moral Principles of Fertility Control
by Denis O'Callaghan DD
pp 39 2s 6d
Dublin: Clonmore & Reynolds Ltd
London: Burns Oates Ltd 1961
This booklet sets out the Roman Catholic position on birth control including oral contraception.

The following books have also been submitted for review:

Farr A D
A laboratory handbook of blood transfusion techniques
pp xi+135 17s 6d
London: Heinemann 1961

Finerty J C & Cowdry E V
A textbook of histology: functional significance of cells and intercellular substances
5th ed pp 573 82s 6d
London: Kimpton 1960

Hazell K
Social and medical problems of the elderly
pp 216 30s
London: Hutchinson 1960

Hospital Abstracts
A monthly survey of world literature prepared by the Ministry of Health
vol 1, no 1 Abstracts 1–154 January 1961
pp 68+iv 5s
London: HMSO 1961
This is a compound of abstracts on the administration of hospitals

Thorek M
Surgical errors and safeguards
5th ed pp xvi+652 £10
London: Pitman 1960

Vass C C N ed
A synopsis of physiology (Rendle Short)
5th ed pp 348 30s
Bristol: Wright 1961